Memorial Sloan Kettering Cancer Center

# CNS metastases: Multidisciplinary Tumor Board Case Presentation

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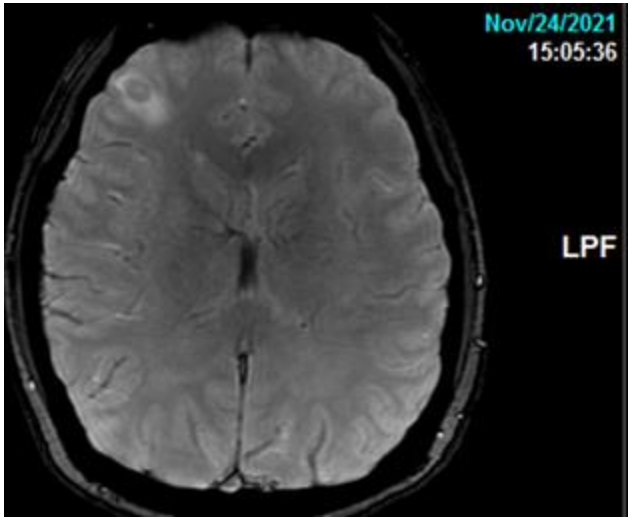
6th Annual Breast Cancer Symposium
"*Yesterday, Today, and Tomorrow*"
October 19, 2024

# Case Presentation (1)

- 40 yo F presents with cT3N2 ER-/PR-/HER2 3+ L breast cancer.
- Received neoadjuvant ddAC-THP
- At surgery ypT2N1 (3.2cm + 3+ axillary nodes).
- Adjuvant trastuzumab emtansine started, adjuvant radiation delivered.

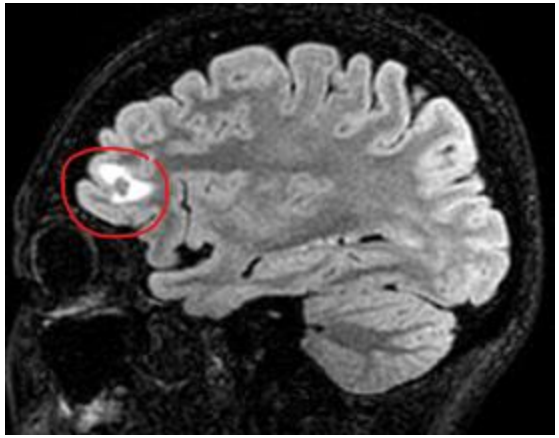
4 months into adjuvant trastuzumab emtansine, patient felt headache and "woozy". An MRI of the brain was performed.



# Case Presentation (2)

- A PET/CT scan showed no evidence of non-CNS progression
- SRS was planned after multidisciplinary discussion at the weekly MSK Brain Metastasis Tumor Board
- Trastuzumab emtansine was continued
- Symptoms resolved, and initial follow-up MRI showed improvement in the frontal lobe metastasis.

3 months later, the patient experienced headache again and follow-up MRI was performed.

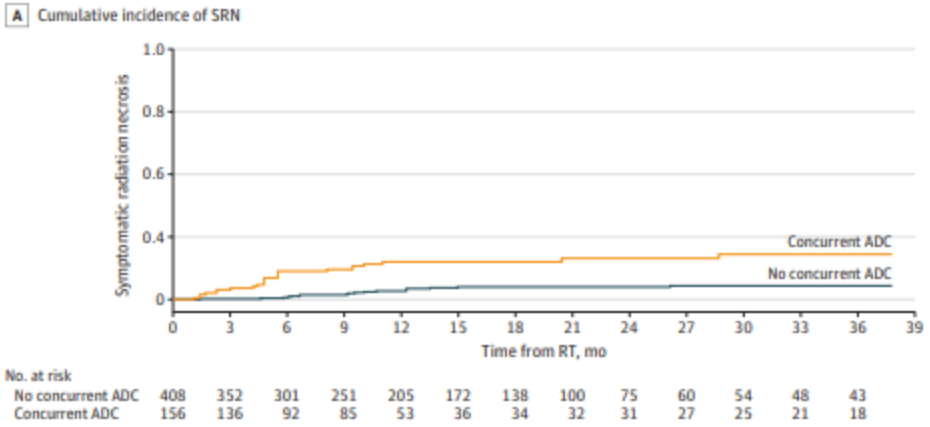


# Symptomatic necrosis with antibody-drug conjugates and concurrent stereotactic radiotherapy for brain metastases

**Table. Baseline Patient and Treatment Characteristics**

| Characteristic | Patient group[a] Concurrent ADC | No concurrent ADC | All (N = 98) |
|---|---|---|---|
| **Patients** | | | |
| Age, median (range), y[b] | 54 (27-77) | 55 (34-77) | 55 (27-77) |
| Sex | | | |
| Women | 33/42 (78.6) | 66/74 (89.2) | 82/98 (83.7) |
| Men | 9/42 (21.4) | 8/74 (10.8) | 16/98 (16.3) |
| Primary cancer diagnosis | | | |
| Breast | 30/42 (71.4) | 55/74 (74.3) | 71/98 (72.4) |
| Non-small cell lung cancer, *ERBB2* variant | 4/42 (9.5) | 11/74 (14.9) | 13/98 (13.3) |
| Esophageal and/or gastric cancer, *ERBB2* amplified | 2/42 (4.8) | 4/74 (5.4) | 6/98 (6.1) |
| Salivary, *ERBB2* amplified | 3/42 (7.1) | 2/74 (2.7) | 4/98 (4.1) |
| Other[c] | 3/42 (7.1) | 2/74 (2.7) | 4/98 (4.1) |
| ADC received[d] | | | |
| Trastuzumab emtansine | 21/42 (50.0) | 43/74 (58.1) | 52/98 (53.1) |
| Trastuzumab deruxtecan | 14/42 (33.3) | 42/74 (56.8) | 50/98 (51.0) |
| Sacituzumab govitecan | 7/42 (16.7) | 23/74 (31.1) | 26/98 (26.5) |
| **SRT course** | | | |
| No. of BrM radiated per course | | | |
| 1 | 17/49 (34.7) | 35/122 (28.7) | 52/171 (30.4) |
| 2 | 12/49 (24.5) | 32/122 (26.2) | 42/171 (24.6) |
| 3 | 5/49 (10.2) | 17/122 (13.9) | 22/171 (12.9) |
| 4 | 6/49 (12.2) | 10/122 (8.2) | 15/171 (8.8) |
| ≥5 | 9/49 (18.4) | 28/122 (23.0) | 37/171 (21.6) |
| **Metastasis and treatment** | | | |
| Lesion volume, median (range), cm[3] | 0.30 (0.01-43.15) | 0.25 (0.01-15.6) | 0.26 (0.01-43.15) |
| RT dose and fractionation | | | |
| 21 Gy/1 fraction | 103/156 (66.0) | 230/408 (56.4) | 333/564 (59.0) |
| 18 Gy/1 fraction | 7/156 (4.5) | 71/408 (17.4) | 78/564 (13.8) |
| 27 Gy/3 fractions | 19/156 (12.2) | 73/408 (17.9) | 92/564 (16.3) |
| 30 Gy/5 fractions | 24/156 (15.4) | 25/408 (6.1) | 49/564 (8.7) |
| Other[e] | 3/156 (1.9) | 9/408 (2.2) | 12/564 (2.1) |
| Any prior radiation[f] | 20/156 (12.8) | 81/408 (19.9) | 101/564 (17.9) |
| WBRT | 11/156 (7.1) | 54/408 (13.2) | 65/564 (11.5) |
| Adjacent SRS[g] | 7/156 (4.5) | 38/408 (9.3) | 45/564 (8.0) |
| On-target SRS | 3/156 (1.9) | 1/408 (0.2) | 4/564 (0.7) |

**Figure. Incidence of Symptomatic Radiation Necrosis (SRN) for Brain Metastasis From the Start of Radiotherapy, Stratified by Receipt of Concurrent Antibody-Drug Conjugates (ADC)**



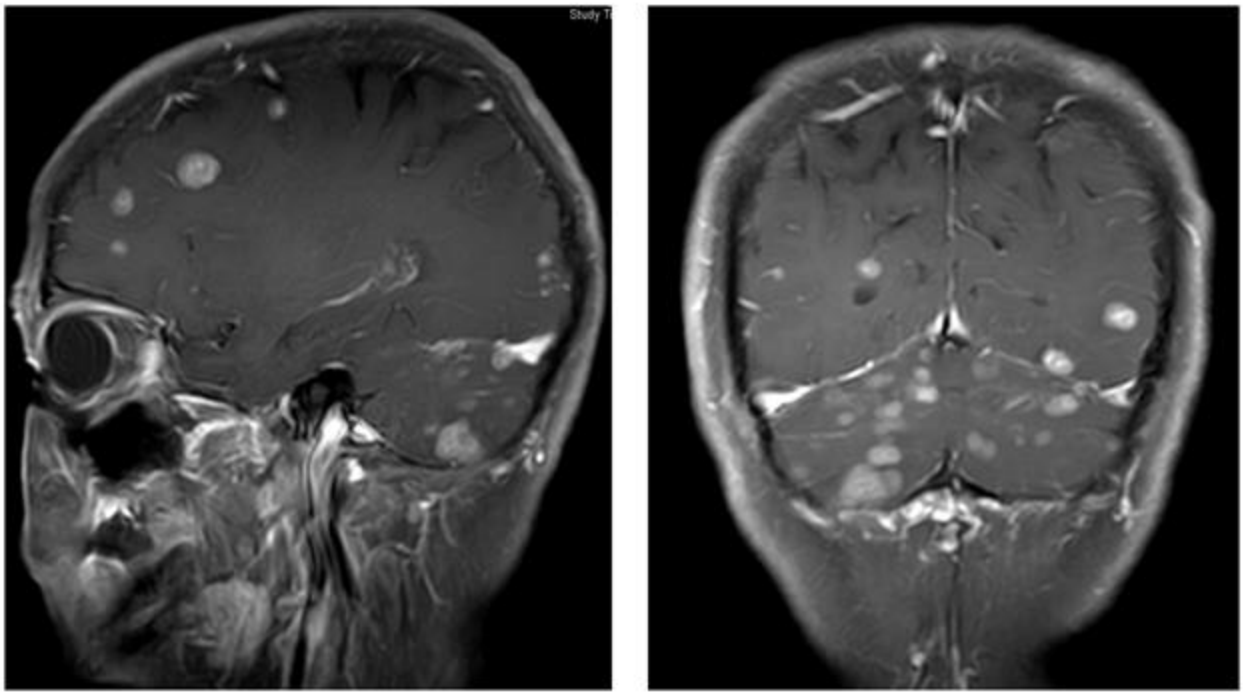

**24 month risk of symptomatic radionecrosis:**

No concurrent (within 3 wks) ADC: 9.4%

Concurrent ADC: 42%

# Case Presentation (3)

- RN was managed with short course of corticosteroids with resolution
- Patient completed adjuvant trastuzumab emtansine
- 1 year later, she developed dizziness and gait instability, and brain MRI revealed further CNS progression, without non-CNS disease.



# Treatment Options Discussed at Brain Metastases Tumor Board

- SRS to 3 larger supratentorial lesions and to posterior fossa
- Whole brain RT
- Systemic therapy alone and careful observation
  - tucatinib/capecitabine/trastuzumab
- SRS to 3 larger supratentorial lesions and to posterior fossa followed by tucatinib/capecitabine/trastuzumab as "secondary prevention"

**Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study**

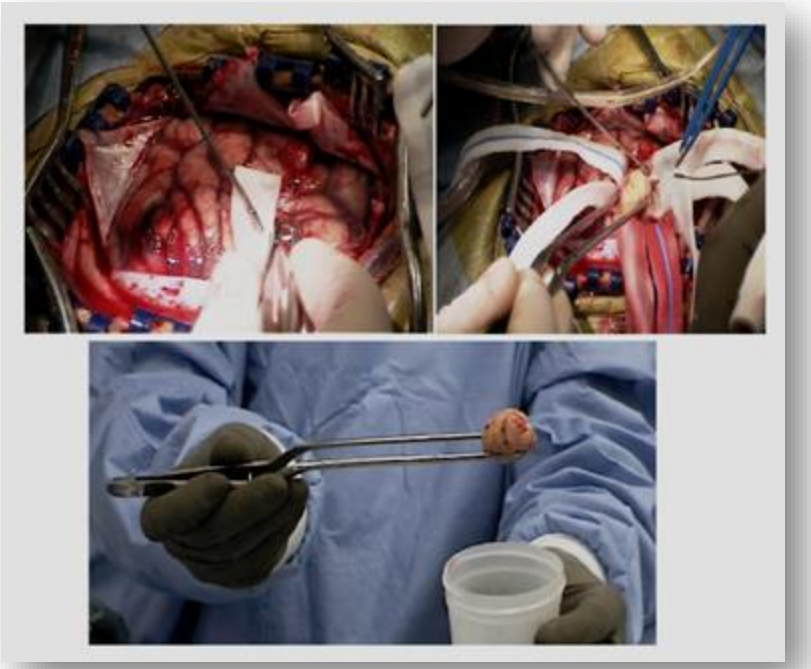
*Thomas Bachelot, Gilles Romieu, Mario Campone, Véronique Diéras, Claire Cropet, Florence Dalenc, Marta Jimenez, Emilie Le Rhun, Jean-Yves Pierga, Anthony Gonçalves, Marianne Leheurteur, Julien Domont, Maya Gutierrez, Hervé Curé, Jean-Marc Ferrero, Catherine Labbe-Devilliers*

57% of patients were symptomatic, 43% asymptomatic
66% response rate, median PFS 6 months

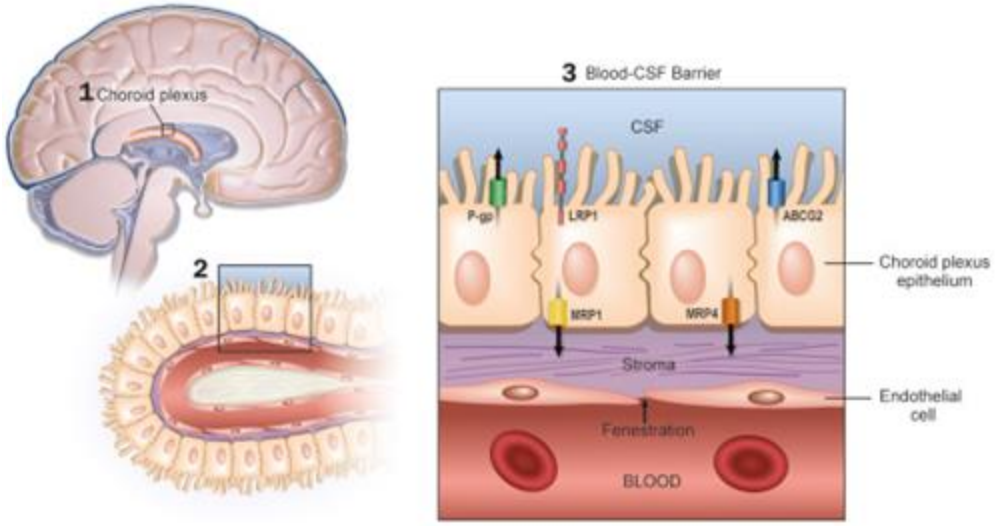
# Case Presentation (4)

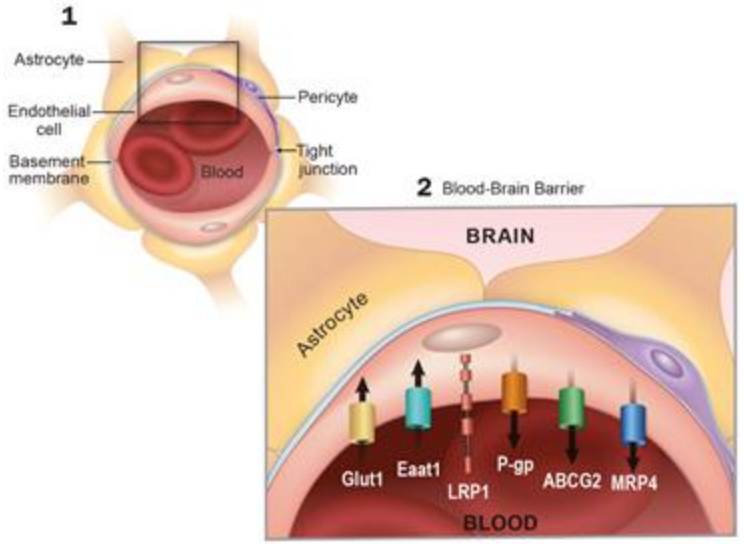
- Patient underwent posterior fossa RT and SRS to the three dominant supratentorial lesions, and started tucatinib/capecitabine and trastuzumab to delay progression/treat non-irradiated smaller supratentorial metastases.
- After initial response in all lesions, she subsequently progressed 2.3 years later with a large temporal metastasis measuring 4.5cm, with edema, with midline shift.
- She was felt to be appropriately managed with neurosurgical resection.

# Historical Management of Breast Cancer Brain Metastases: Reliance on Locoregional Intervention



# CNS: A privileged compartment




Tight junctions
PGP
ABC proteins

ABCB1 and ABCG2 Contribute to limited CNS accumulation of TKI



O'Sullivan CC et al. Semin Oncol 2017
Steeg, Nature Reviews 2021

# Current treatment "algorithm" for HER2+ MBC: Lines of therapy

- **First**: taxane + trastuzumab + pertuzumab
- **Second**: trastuzumab deruxtecan
- **Third**: capecitabine + trastuzumab + tucatinib *or* trastuzumab emtansine
- **Beyond**: Continue trastuzumab with other cytotoxic agents

# Brain Metastases in HER2+breast cancer

- 40-50% of pts with HER2 + MBC develop brain metastases
- Higher mortality
- Morbidity/QoL impact

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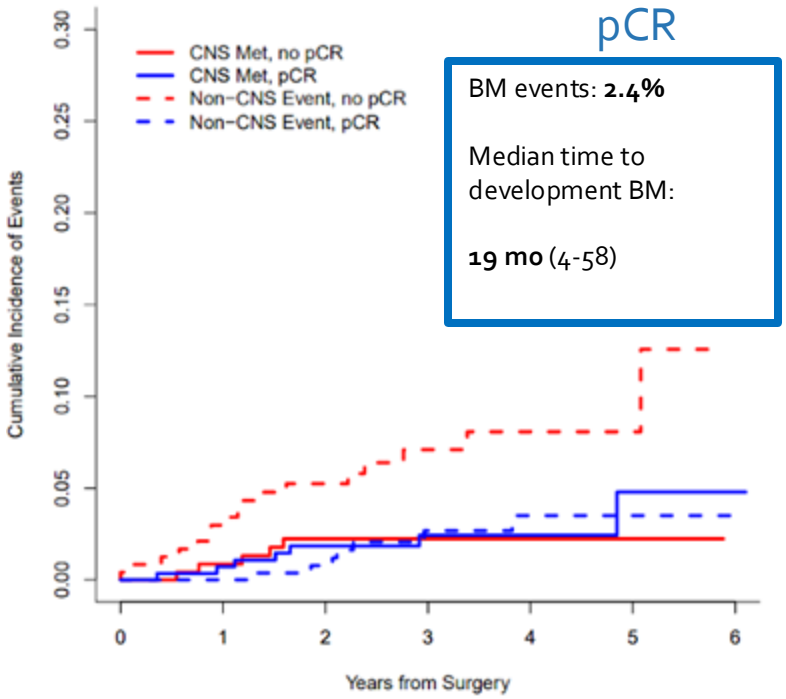
Pestalozzi et al, Lancet Oncol 2013
Morikawa et al, Clin Breast Cancer 2018
Lin et al, Cancer 2008

# Incidence of Brain Metastases after Early HER2+ Breast Cancer: Not Associated with pCR to Neoadjuvant Rx




| pCR | non-pCR |
|---|---|
| BM events: **2.4%**<br><br>Median time to development BM:<br><br>**19 mo** (4-58) | BM events: **2.0%**<br><br>Median time to development BM:<br><br>**6.5 mo** (6.5-17) |

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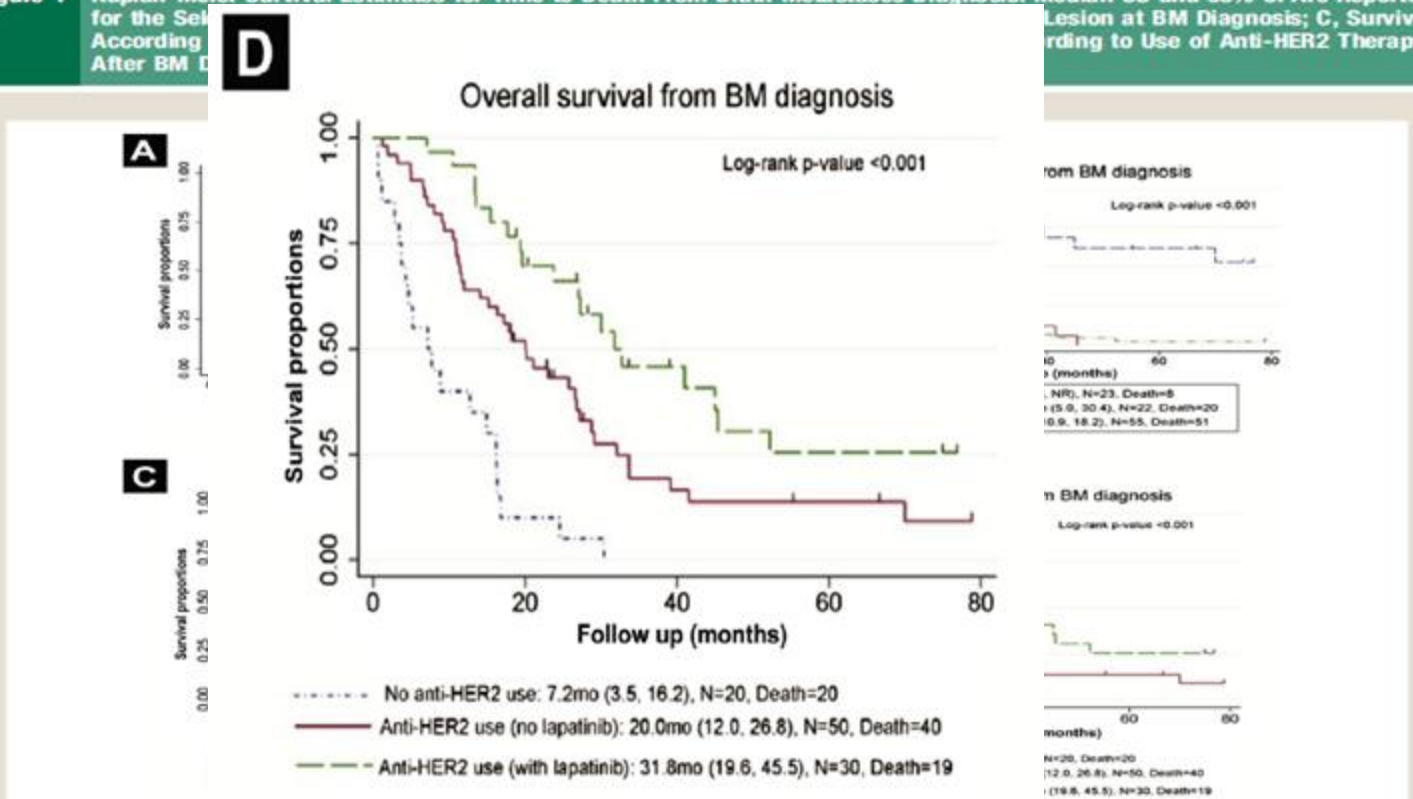
Ferraro E et al NPJ Breast Cancer 8:37, 2022

# Outcomes for HER2+ BCBMs at MSKCC: Signal for Improved Outcomes in the TKI Era

HER2-positive Breast Cancer With Brain Metastases

**Figure 1** Kaplan-Meier Survival Estimates for Time to Death From Brain Metastases Diagnosis. Median OS and 95% CI Are Reported for the Sel… Lesion at BM Diagnosis; C, Survival According … rding to Use of Anti-HER2 Therapy After BM D…



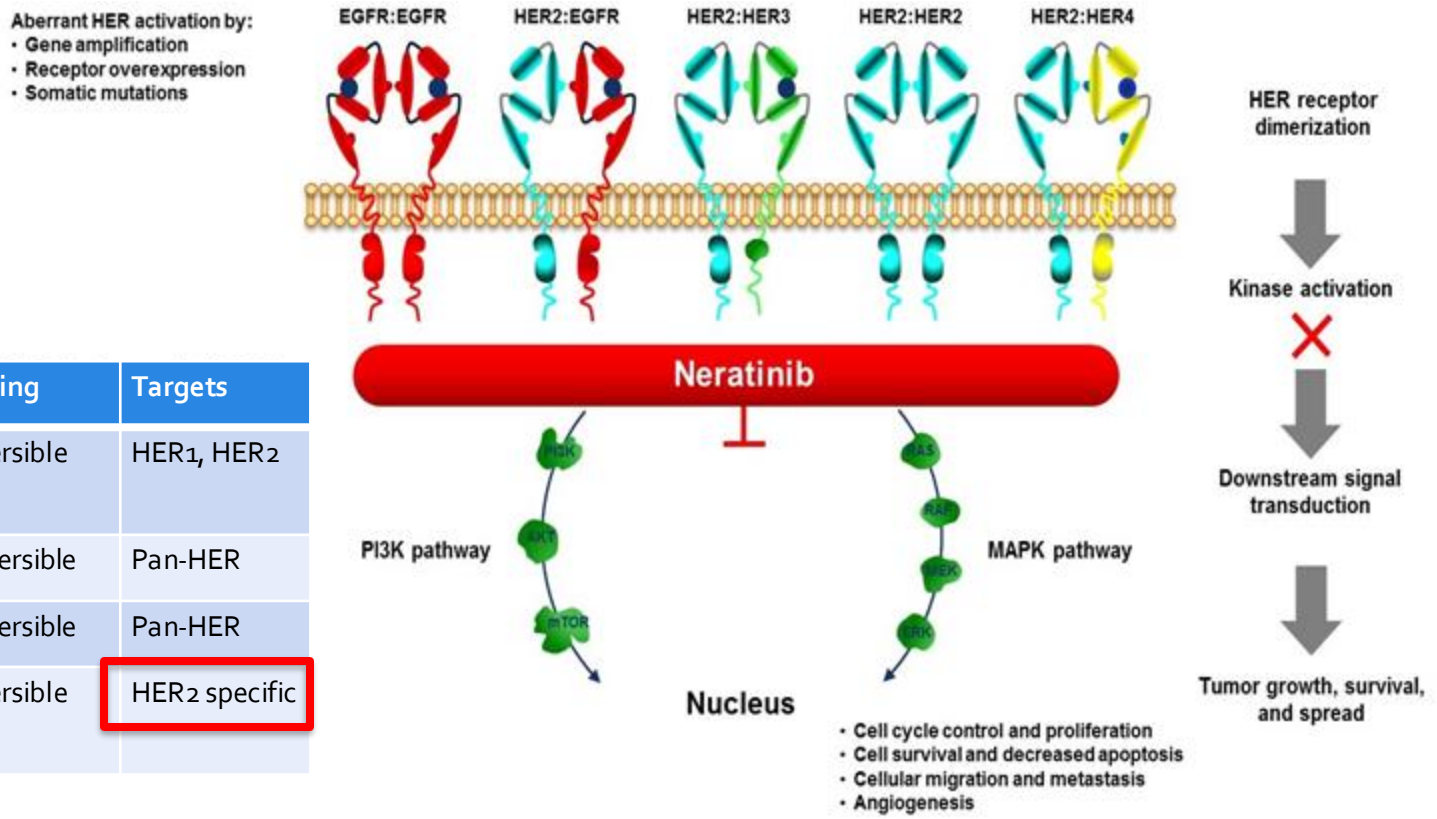

Abbreviations: BM = brain metastases; CI = confidence intervals; NR = not reached; N = number of patients; OS = overall survival.



Morikawa A…Seidman AD. Clin Breast Cancer 18(5):353-61,2018

# HER2-targeted tyrosine kinase inhibitors

| | Binding | Targets |
|---|---|---|
| Lapatinib | Reversible | HER1, HER2 |
| Neratinib | Irreversible | Pan-HER |
| Pyrotinib | Irreversible | Pan-HER |
| Tucatinib | Reversible | HER2 specific |



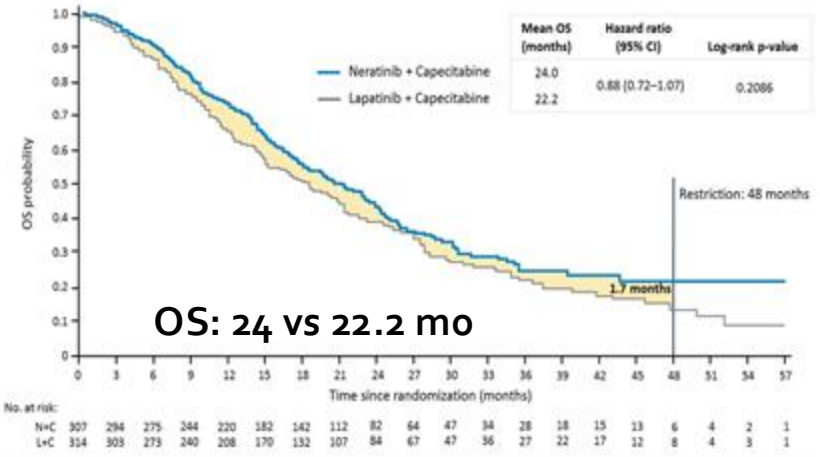
# TKI efficacy for HER2+ breast cancer BM

| Study | Agent | N | CNS ORR | TTP/PFS |
|---|---|---|---|---|
| Lin et al JCO 2008 | **Lapatinib** | 39 | **2.6% (RECIST)**<br>**5.2% (50% volumetric reduction)** | 3.0 mo |
| Lin et al CCR 2008 | **Lapatinib**<br>**Lapatinib/cape** | 237*<br>50 | **6% (composite criteria)**<br>**20% (optional extension)** | 2.4 mo<br>3.6 mo |
| Freedman et al. 2016 and 2019 | **Neratinib/cape** | Pre-rx: 40<br>Lap Naïve: 49<br>Lap treat: 12 | **8%**<br>**49%(RECIST 1.1)**<br>**33%** | 1.9 mo<br>5.5 mo<br>3.1 mo |
| Lin at al 2020 | **Tucatinib/H/ cape** | Stable: 80<br>Active: 55<br>Untreated: 44 | **NA**<br>**47.3%(RECIST 1.1)**<br>**47.1% (RECIST 1.1)** | 13.9 mo**<br>9.5 mo<br>8.1 mo |
| Yan et al ASCO 2021 | **Pyrotinib/cape** | 59 (RT-naive)<br>19 (POD to RT) | **74.6%**<br>**42.1%** | 12.1 mo<br>5.6 mo |

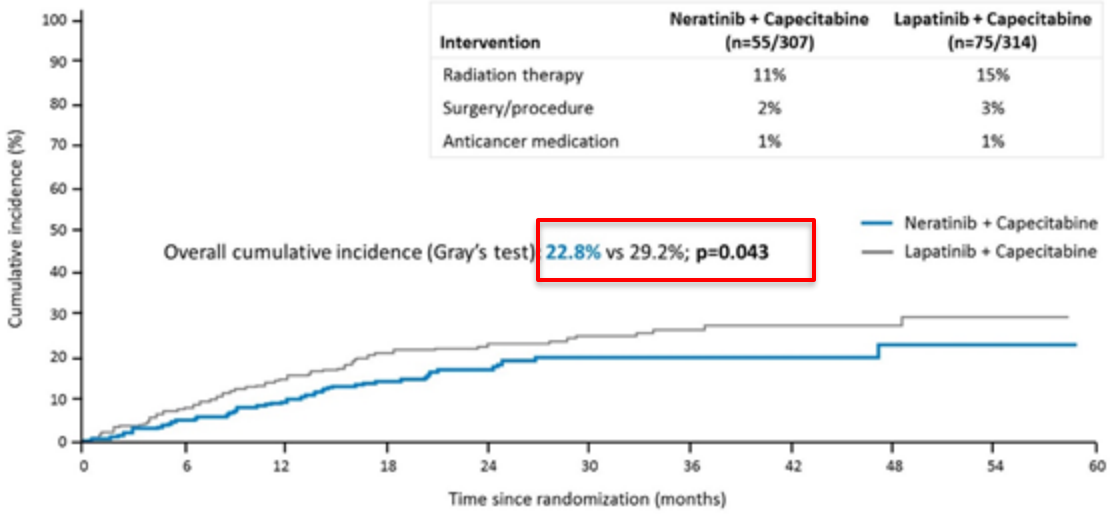


*mITT population
** **CNS**-PFS

# Neratinib vs Lapatinib: NALA Trial




| Intervention | Neratinib + Capecitabine (n=55/307) | Lapatinib + Capecitabine (n=75/314) |
|---|---|---|
| Radiation therapy | 11% | 15% |
| Surgery/procedure | 2% | 3% |
| Anticancer medication | 1% | 1% |






Saura et al. JCO 2020

correspondence

# Comparative Effectiveness Research Needs to Consider Optimal Dosing and Scheduling

## TO THE EDITOR:

In their report of the NALA trial, Saura et al[1] describe incremental improvement in control of CNS and non-CNS human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer for neratinib over lapatinib, both administered continuously, together with concurrent conventionally dosed capecitabine. Their analysis of time to intervention for CNS metastasis is one not commonly reported and could be confounded by factors such as the status of non-CNS disease and even patient preference. Indeed, given the known benefits for dual HER2 inhibition,[2] the absence of trastuzumab in both arms might be expected to increase the likelihood of non-CNS progression. But there is another issue of concern in this study that involves the fundamental design of the treatment arms.

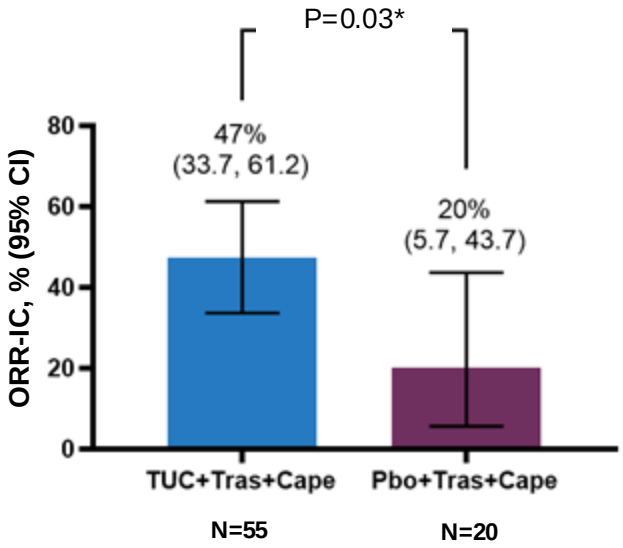
found that a pulsatile, intermittent high dose of lapatinib administered on days one, two, and three, and with capecitabine on days 8-14 of a 14-day cycle was the optimal dose schedule. A clinical trial using this regimen demonstrated substantial activity in metastases in the cerebrum, spinal cord, and leptomeninges.[13]

To extend survival in HER2-driven metastatic breast cancer, systemic agents must control metastases in both the CNS and non-CNS compartments. We applaud the NALA[1] (and HER2CLIMB)[14] investigators on important incremental work in this direction. As further and larger studies are designed, however, we assert that it is imperative to develop and test optimal dose schedules of the HER2-targeting TKIs that are employed, which may not be continuous daily exposure.

**Andrew D. Seidman, MD, Elisa de Stanchina, PhD, and Larry Norton, MD**
*Memorial Sloan Kettering Cancer Center, New York, NY*

**Aki Morikawa, MD**
*University of Michigan, Ann Arbor, MI*

# HER2CLIMB: Preliminary Intracranial Efficacy

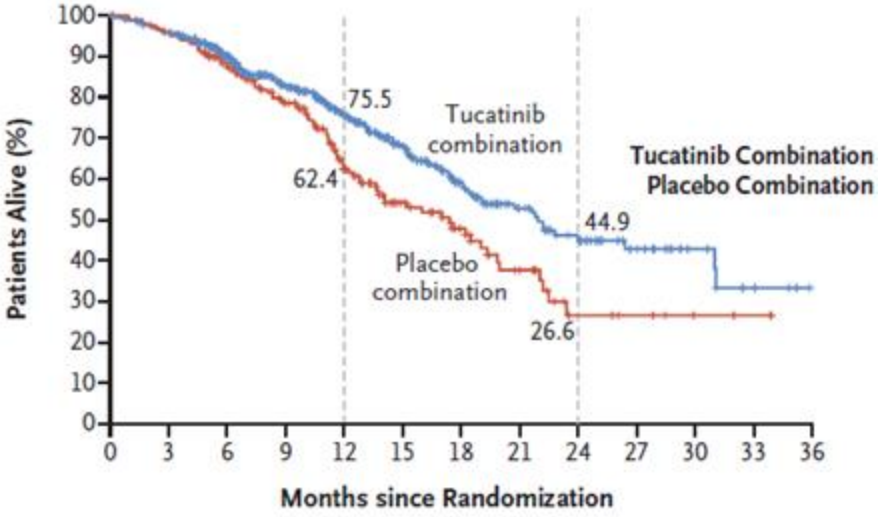



| | TUC+Tras+Cape, (N=55) | Pbo+Tras+Cape, (N=20) |
|---|---|---|
| Patients with Objective Response of Confirmed CR or PR, n | 26 | 4 |
| Confirmed ORR-IC, % (95% CI) | 47.3 (33.7, 61.2) | 20.0 (5.7, 43.7) |
| DOR-IC[a], months (95% CI) | 8.6 (5.5, 10.3) | 3.0 (3.0, 10.3) |

***More frequent and more durable intracranial responses with tucatinib***

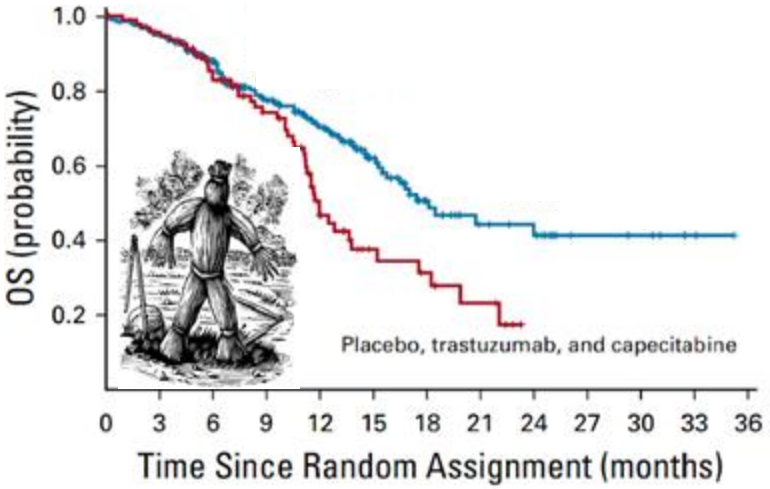
# Overall Survival in HER2-CLIMB
## (comparator arm with No TKI)

OS: 21.9 vs 17.4 mo HR:




**Overall population**

OS: 18.1 vs 12 mo




**Brain Metastases sub-group**

**48.3 % of overall population**
**28.4 % with active CNS disease**



Murthy RK, NEJM 2020
Lin NU, JCO 2020

# Intra-Operative Tumor and Serum Procurement for Studying CNS Drug PK and PD

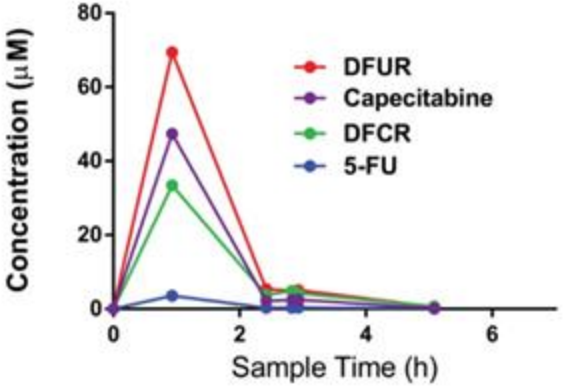
Dr. Viviane Tabar and assisting Neurosurgical Fellow

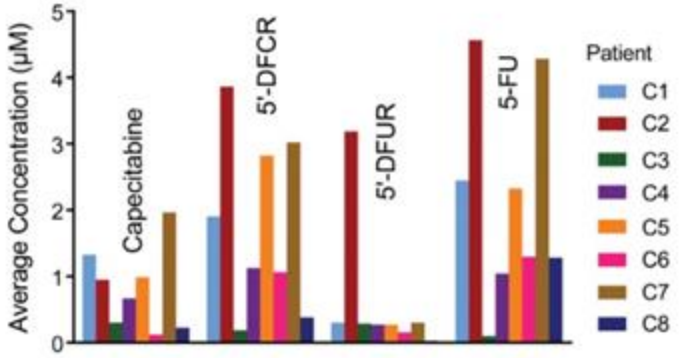
RSAs Akheem Simmons, Brooke Crawford
PI Andrew Seidman

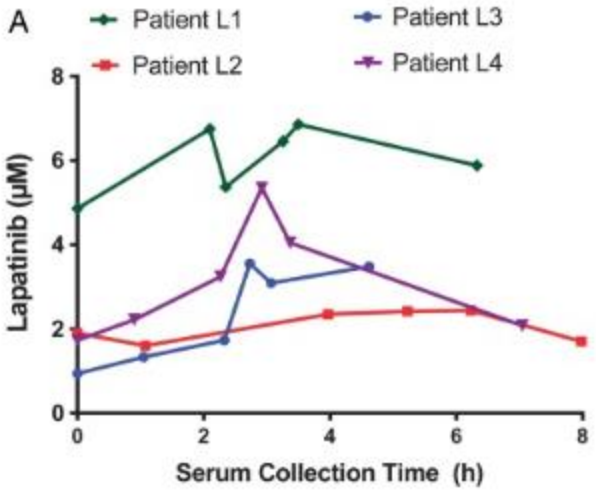
Memorial Sloan Kettering Cancer Center

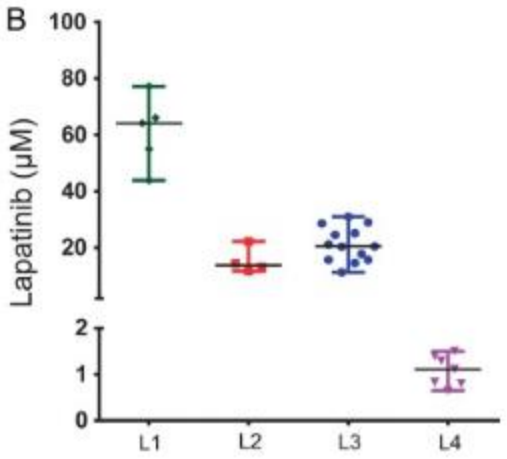
Support: Department of Defense ERA of Hope Center of Excellence Grant

# Therapeutic [5-FU] in brain metastases, Variable and suboptimal [lapatinib]






Morikawa A…Seidman AD. Neuro-oncology 2015

Neuro-Oncology

*Neuro-Oncology* 17(2), 289–295, 2015
doi:10.1093/neuonc/nou141
Advance Access date 11 July 2014

# Capecitabine and lapatinib uptake in surgically resected brain metastases from metastatic breast cancer patients: a prospective study

**Aki Morikawa, David M. Peereboom, Helen R. Thorsheim, Ramakrishna Samala, Rajiv Balyan, Conleth G. Murphy, Paul R. Lockman, Ahkeem Simmons, Robert J. Weil, Viviane Tabar, Patricia S. Steeg, Quentin R. Smith, and Andrew D. Seidman**

*Memorial Sloan-Kettering Cancer Center, New York, New York (A.M., C.G.M., A.S., V.T., A.D.S.); Cleveland Clinic, Cleveland, Ohio (D.M.P., R.J.W.); Texas Tech University Health Sciences Center, Amarillo, Texas (H.R.T., R.S., R.B., P.R.L., Q.R.S.); Center for Cancer Research National Cancer Institute, Bethesda, Maryland (P.S.S.)*

**Corresponding Author:** Andrew D. Seidman, MD, Evelyn Lauder Breast Center, Memorial Sloan-Kettering Cancer Center, 300 East 66th Street, New York, NY 10065 (seidmana@mskcc.org).

***Background.*** Breast cancer brain metastases (BCBM) are challenging complications that respond poorly to systemic therapy. The role of the blood–tumor barrier in limiting BCBM drug delivery and efficacy has been debated. Herein, we determined tissue and serum levels of capecitabine, its prodrug metabolites, and lapatinib in women with BCBM resected via medically indicated craniotomy.

***Methods.*** Study patients with BCBM requiring surgical resection received either single-dose capecitabine (1250 mg/m$^2$) 2–3 h before surgery or 2–5 doses of lapatinib (1250 mg) daily, the last dose 2–3 h before surgery. Serum samples were collected serially on the day of surgery. Drug concentrations were determined in serum and BCBM using liquid chromatography tandem mass spectrometry.

***Results.*** Twelve patients were enrolled: 8 for capecitabine and 4 for lapatinib. Measurable drug levels of capecitabine and metabolites, 5′-deoxy-5-fluorocytidine, 5′-deoxy-5-fluorouridine, and 5-fluorouracil, were detected in all BCBM. The ratio of BCBM to serum was higher for 5-fluorouracil than for capecitabine. As for lapatinib, the median BCBM concentrations ranged from 1.0 to 6.5 μM. A high variability (0.19–9.8) was noted for lapatinib BCBM-to-serum ratio.

***Conclusions.*** This is the first study to demonstrate that capecitabine and lapatinib penetrate to a significant though variable degree in human BCBM. Drug delivery to BCBM is variable and in many cases appears partially limiting. Elucidating mechanisms that limit drug concentration and innovative approaches to overcome limited drug uptake will be important to improve clinical efficacy of these agents in the central nervous system. Trial registration ID: NCT00795678.

# Pulsatile High Dose EGFR-TKI in NSCLC Brain Metastases

- [Erlotinib] in CSF with standard dosing inadequate to kill EGFR mutant NSCLC cells[1]
- Pulsatile high-dose weekly erlotinib active in EGFR mutant NSCLC CNS metastases progressing despite conventional dose erlotinib[2]
- High dose gefitinib or erlotinib effective in non-CNS sites in EGFR-mut NSCLC pts with resistance to standard dose[3]
- Pulsatile high dose erlotinib and gefitinib increased CSF levels[4]

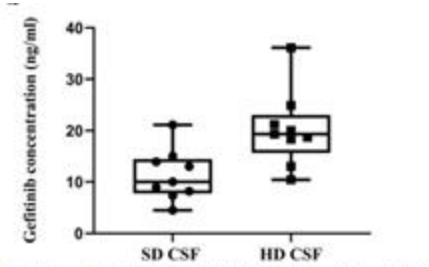



Fig. 2 Distribution of gefitinib at standard dose (250 mg OD) and high dose (1250 mg OD) in plasma (a) and CSF (b) (n = 9 for standard dose and high dose)

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[1]Clarke JL et al J Neurooncol 2010
[2]Grommes C et al Neurooncol 2011
[3]Zhu Y et al Thoracic Cancer 2016
[4]Shriyan B et al Eur J Clin Pharmacol 2020

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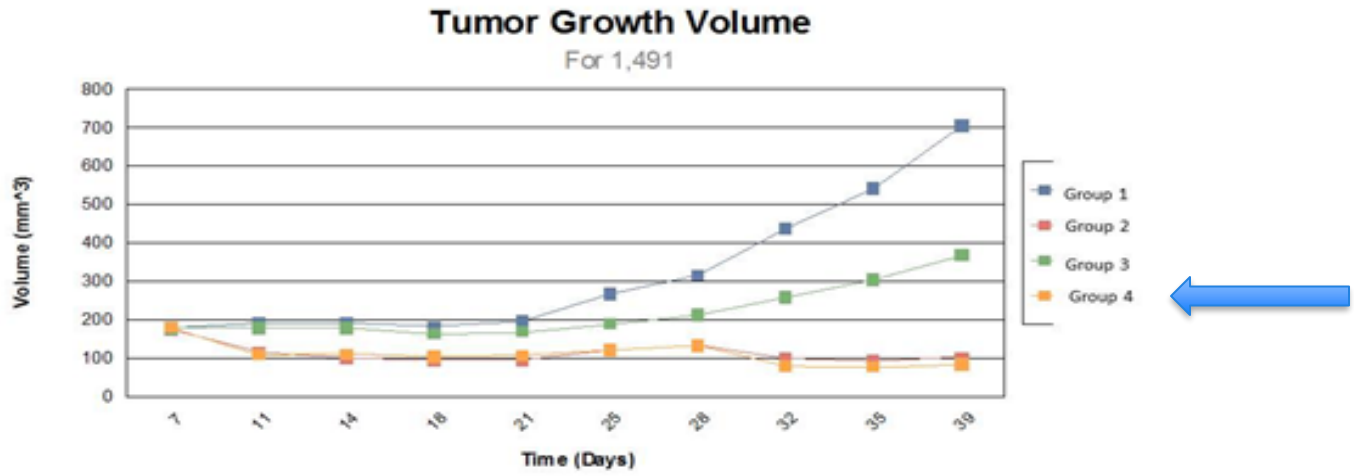
# Pulsatile High Dose Lapatinib 3 days on 11 days off may be optimal in tandem with capecitabine




**The group with intermittent lapatinib at high dose (800mg/kg) in tandem with capecitabine 500mg/kg 7 days on/days off tolerated the treatment regimen that showed anti-tumor efficacy, but the group with intermittent high dose lapatinib and capecitabine administered concurrently did not tolerate the regimen and was unable to be evaluated for anti-tumor efficacy.**

Morikawa A…Seidman AD. Neuro-Oncol 17(2):289-95, 2015

Published OnlineFirst April 15, 2019; DOI: 10.1158/1078-0432.CCR-18-3502

Clinical Trials: Targeted Therapy

Clinical Cancer Research

# Phase I Study of Intermittent High-Dose Lapatinib Alternating with Capecitabine for HER2-Positive Breast Cancer Patients with Central Nervous System Metastases

Aki Morikawa[1], Elisa de Stanchina[2], Elena Pentsova[3], Margaret M. Kemeny[4], Bob T. Li[5], Kendrick Tang[5], Sujata Patil[6], Martin Fleisher[7], Catherine Van Poznak[1], Larry Norton[5], and Andrew D. Seidman[5]

## Abstract

**Purpose:** Lapatinib and capecitabine cross the blood–tumor barrier in breast cancer brain metastasis but have modest clinical efficacy. Administration of high-dose tyrosine kinase inhibitor has been evaluated in brain metastases and primary brain tumors as a strategy to improve drug exposure in the central nervous system (CNS). We derived a rational drug scheduling of intermittent high-dose lapatinib alternating with capecitabine based on our preclinical data and Norton–Simon mathematical modeling. We tested this intermittent, sequential drug schedule in patients with breast cancer with CNS metastasis.

**Patients and Methods:** We conducted a phase I trial using an accelerated dose escalation design in patients with HER2-positive ($HER2^+$) breast cancer with CNS metastasis. Lapatinib was given on day 1–3 and day 15–17 with capecitabine on day 8–14 and day 22–28 on an every 28-day cycle. Lapatinib dose was escalated, and capecitabine given as a flat dose at 1,500 mg BID. Toxicity and efficacy were evaluated.

**Results:** Eleven patients were enrolled: brain only (4 patients, 36%), leptomeningeal (5 patients, 45%), and intramedullary spinal cord (2 patients, 18%). Grade 3 nausea and vomiting were dose-limiting toxicities. The MTD of lapatinib was 1,500 mg BID. Three patients remained on therapy for greater than 6 months.

**Conclusions:** High-dose lapatinib is tolerable when given intermittently and sequentially with capecitabine. Antitumor activity was noted in both CNS and non-CNS sites of disease. This novel administration regimen is feasible and efficacious in patients with $HER2^+$ breast cancer with CNS metastasis and warrants further investigation.

Memorial Sloan Kettering Cancer Center

# WinHER2 Study
# IRB 22-168

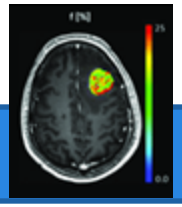
## Window Of Opportunity Study of Preoperative Tucatinib In Patients with HER2+ Brain Metastases

PI: Seidman AD
Co-PI: Moss N
Advanced Oncology Research Fellow: Ferraro E

# WinHER2 Study schema

Patients with need of surgical resection of brain metastasis in HER2+ or mutant metastatic cancer

Dr. Holodny
Dr. Young



DCE MRI and correlation with PK


-4 d -3 d -2 d -1 d

Surgery

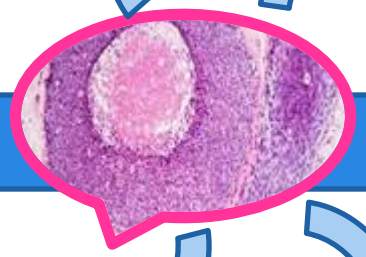
Plasma/serum samples for drug PK

**Primary endpoint:** Drug PK: CNS mets samples for intratumoral, plasma, surrounding brain and CSF drug concentration

De Stanchina Lab

Dr Wilcox

CSF cytology, CSF CTC, cfDNA

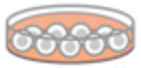


IHC/FISH and EM analysis of TJ and elements of BTB

IGO/Weigelt Lab

WGS and scRNAseq

Dr. Milner, WCMC



Isogenic cell models based on new resistance mutations

Chandarlapaty lab

**Cohort A (N=10)**
CNS POD while on tucatinib

**Cohort B (N=10)**
tucatinib-naive patients

**Cohort C (N=8)**
HER2 mut BC, HER2+/mut lung, colorectal and gastroesophageal cancer

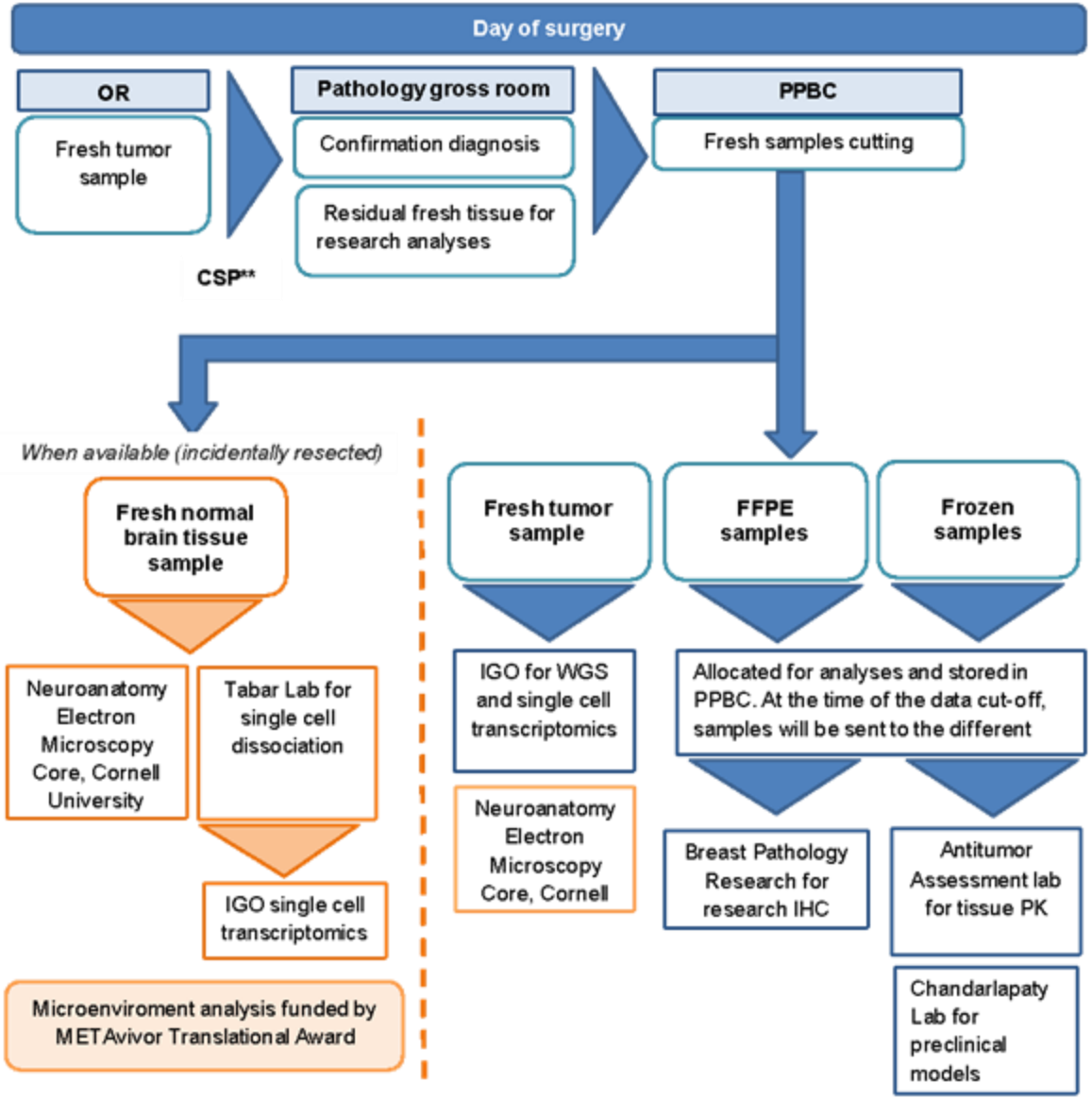
Dr. Li
Dr. Cytryn

Microenvironment sub-study (2023 METAVIVOR translational award): exploring cell elements of the tissue surrounding the BrM using EM and scRNA sequencing

Memorial Sloan Kettering Cancer Center

CNS: central nervous system; CSF: cerebrospinal fluid; CTC: circulating tumor cells; POD: progression of disease; PK: pharmacokinetic; TJ: tight junctions; BTB: brain tumor barrier; EM: electron microscopy

**APPENDIX C. Flow chart of brain metastases samples procurement and shipping ***



# Primary Objective

To evaluate and compare PK of tucatinib by measurement of intratumoral and intertumoral brain metastases (in case of more than 1 metastases resected) and plasma levels in HER2 positive breast cancer with progressing BM while on tucatinib (resistant) (Cohort A) and in tucatinib naïve (sensitive) patients (Cohort B)

- [tucatinib] in the brain samples
- Ratio plasma/brain tissue
- Ratio CSF/brain tissue *

Hypothesis: the development of tucatinib resistance may be associated with sub-therapeutic tucatinib concentration/CNS penetration

**<u>In house PK analysis: De Stanchina Lab (Vanessa Thompson)</u>**

* CSF analysis is optional, expected patients N=10

# Secondary Objectives

- PK analysis of Cohort C
- To evaluate Genomic (WGS) and Transcriptomic (scRNAseq) landscape of BM to evaluate putative mechanism(s) of resistance
- To compare genomic profile in the brain metastasis with plasma cfDNA and CSF cfDNA (the latter when available)
- To explore the association between PK and:
  - Efflux pump expression including Pgp, ABCB1 and ABCG2 in human brain micro-vessels by immunohistochemistry (IHC)
  - Immune biomarkers via IHC
  - Microenvironment element and tight junction integrity and via electron microscopy *(Dr. Theresa Milner, Neuropathology, Cornell)*
  - Perfusion DCE MRI K*trans* and VP
- Safety of preoperative administration of tucatinib

Exploratory objective: CNS-PFS in patients enrolled in cohort B and cohort C who will continue tucatinib beyond the study period (at the discretion of their treating physician)

# PK representation

Convert plasma and tissue concentration both in nmol/L

Tucatinib: Molecular Weight. 480.5 g/mol

Ratio brain/plasma (calculate as mean of the time points)

Known = IC50: 275 ng/ml (8 nmol) for HER2 inhibition

https://www.sciencedirect.com/science/article/pii/S0923753420398355?via%3Dihub#bib11

Preclinical and clinical evaluation of the effect of gastric pH on exposure of ARRY-380 formulated as a crystalline freebase and a PVP-VA spray dried dispersion [abstract]

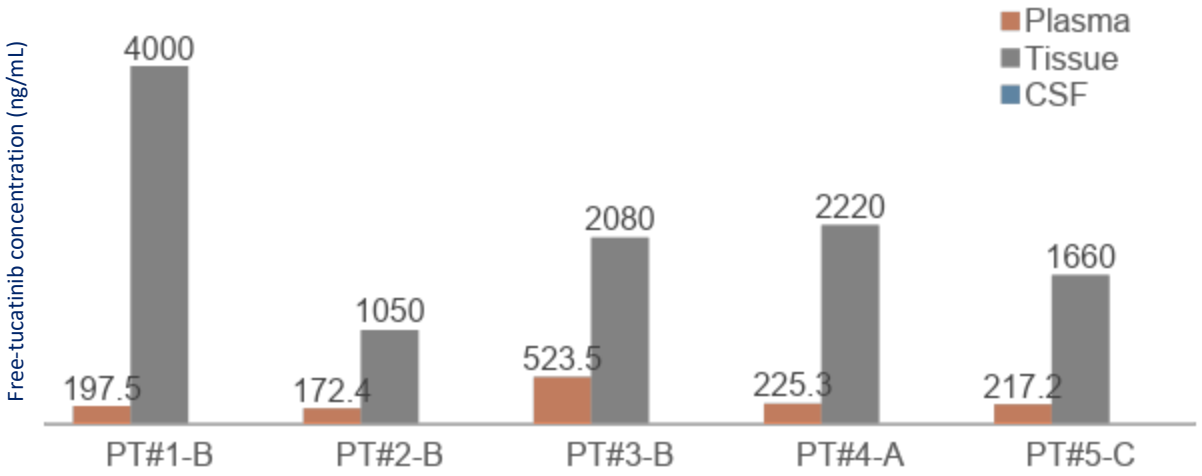
Proceedings of the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition, AAPS, San Antonio, TX (2013) Abstract nr W5276

# Preliminary PK Results

Primary endpoint: tucatinib intracranial penetration

- 5 patients enrolled (all female, median age 48 [41-65])
  - 1 in cohort A (MBC progressing on tucatinib)
  - 3 in cohort B (MBC tucatinib naïve)
  - 1 in cohort C (CRC progressing on tucatinib)

- One resected lesion for each patient localized in the following sites:
  right cerebellar (PT#1-B)*, left cerebellar (PT#2-B)*, left occipital (PT#3-B), left frontal (PT#4-A) and right cerebellar (PT#5-C)




| Cohort | N of patients | BM: plasma ratio (mean) | Standard deviation |
|---|---|---|---|
| A | 1 | 9.8 | - |
| B | 3 | 10.6 | 7.2 |
| C | 1 | 7.6 | - |

Notes: plasma [tucatinib] average concentration of the 4 the timepoints; tissue [tucatinib] expressed ng/ml after approximation of brain density to water density
* Pre-treated with SRS

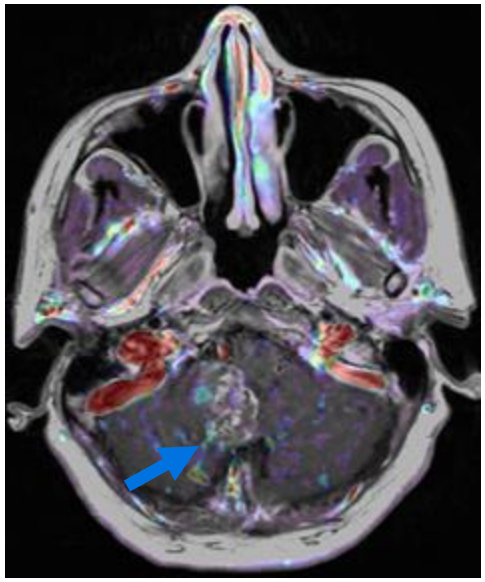
MBC: metastatic breast cancer
CRC: colorectal cancer



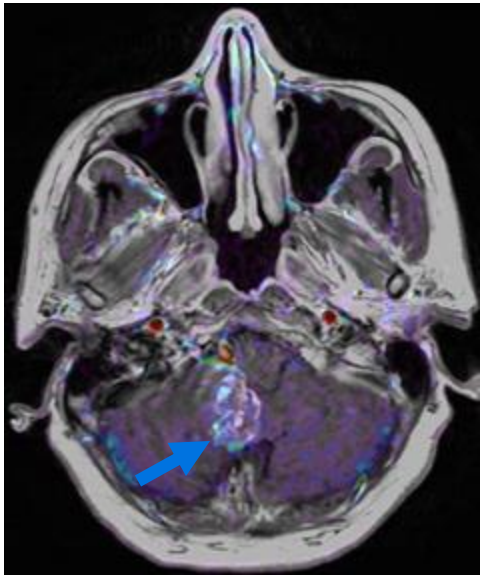
Unpublished data

# Clinical Vignette: PT#5-C

56 yo F with metastatic HER2+ CRC (Fold-Change: 25.6), on 2nd line tucatinib trastuzumab for 11 months, with new diagnosis of right inferior cerebellar lesion of 3 x 2.3 cm



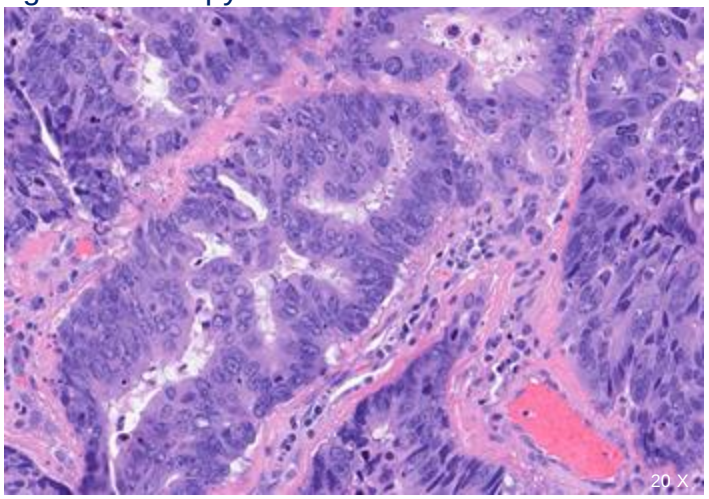
rKtrans: 2.34



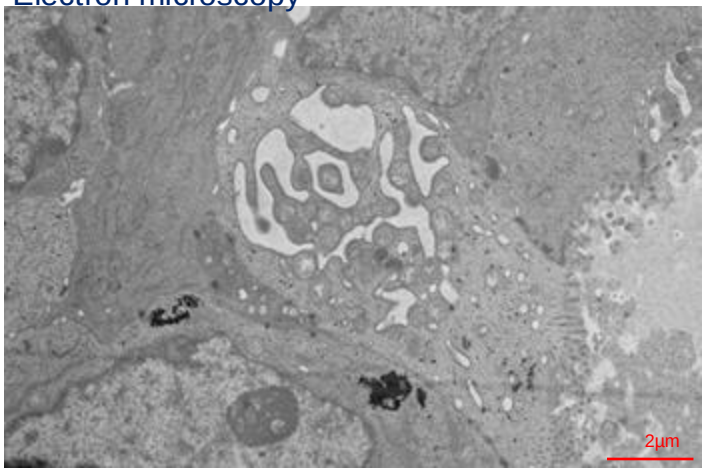
rVP: 6.36

[Tuc]: 1660 ng/mL, tissue/plasma ratio 7.6

Light microscopy




Electron microscopy




Courtesy of Drs: R. Young, M. Rosenblum and T. Milner
Unpublished data

# Frequency of MAPK and PI3K pathway alterations in the first 4 HER2+ resected breast cancer brain metastases


**Findings:**
All patients maintained HER2 amplification in the resected brain metastases
Most common mutations were PIK3CA missense mutations (driver alterations)
One tucatinib-naive patient had EGFR amplification and ERBB3 missense mutations and NF1 loss suggesting that the MAPK pathway is altered in multiple points
**Pending:** Extensive genomic assessment by WGS with the aim to capture potential differences across the cancer genome in BM pre-exposed and naïve to tucatinib.

Legend: Each rectangle is a patient. Column 3 is the unique patient in cohort A (tucatinib resistant); all the other patients are tucatinib-naïve.

# Opportunity to recapitulate pre-clinical data

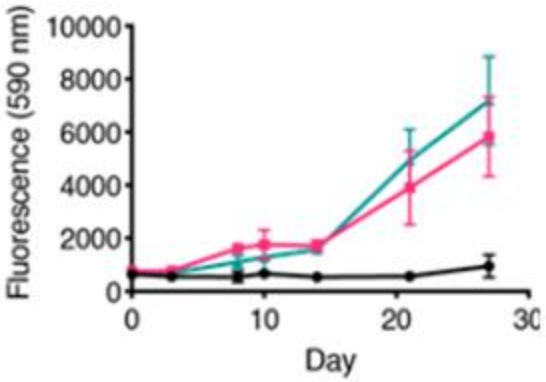
San Antonio Breast cancer Symposium ®, December 7-10, 2021

## Validation

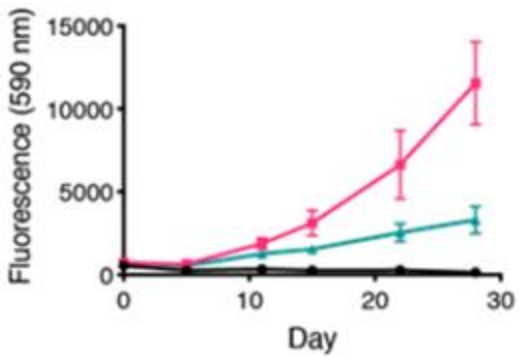
### HER2-TKI resistance in NF1 silenced-cells

Alison Smith

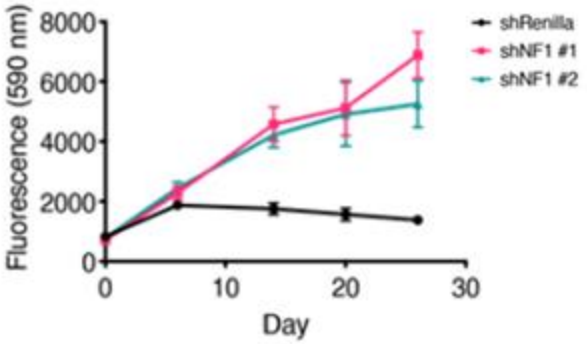
Sarat Chandarlapaty




500 nM of lapatinib




50 nM of neratinib




100 nM of tucatinib

Smith A, et al. Nature Comms 2021.

nature COMMUNICATIONS

ARTICLE

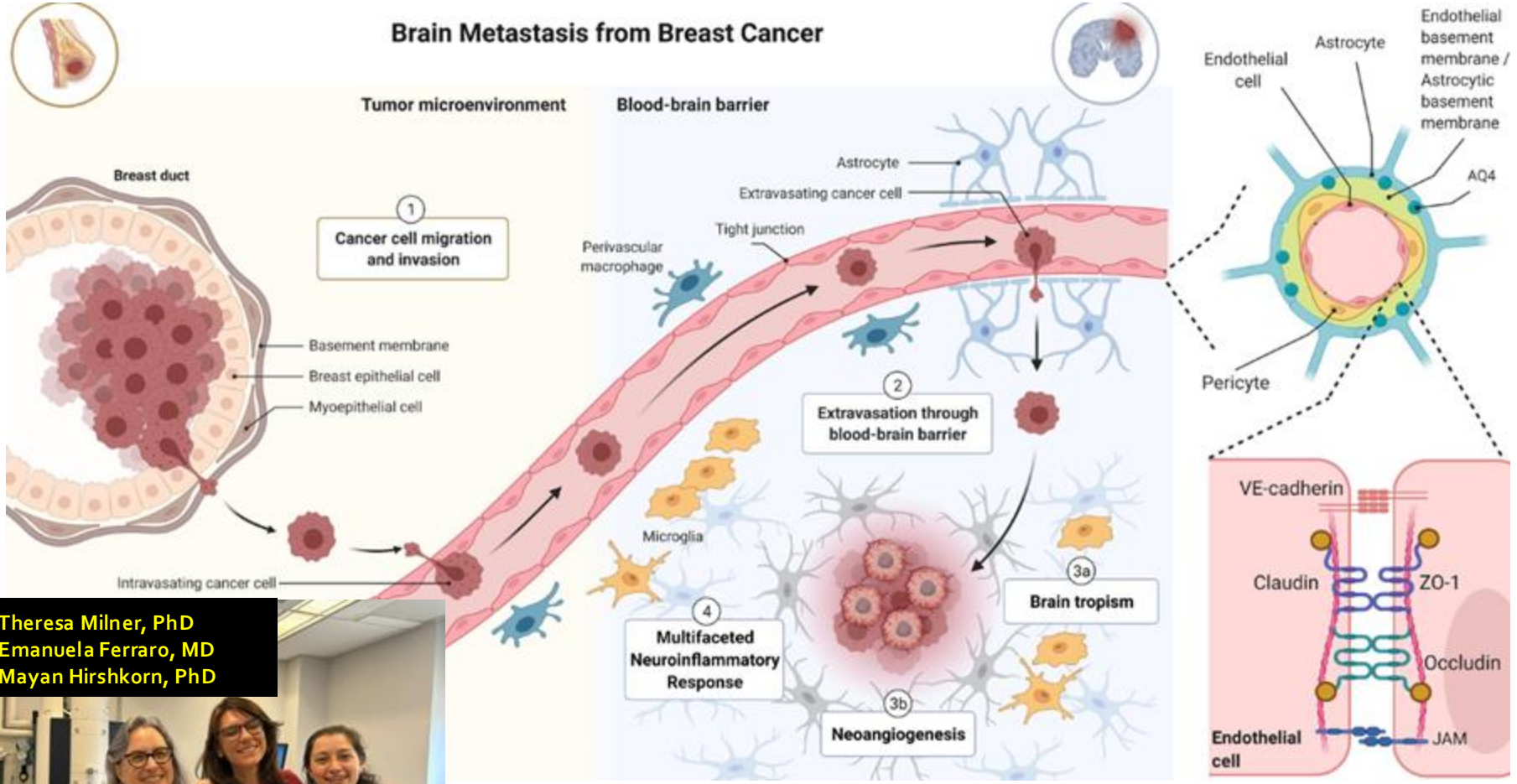
https://doi.org/10.1038/s41467-021-27093-y OPEN

# HER2 + breast cancers evade anti-HER2 therapy via a switch in driver pathway

Alison E. Smith[1,2], Emanuela Ferraro[1,3], Anton Safonov[1,3], Cristina Bernado Morales[4], Enrique J. Arenas Lahuerta[4], Qing Li[1], Amanda Kulick[5], Dara Ross[6], David B. Solit[1,2], Elisa de Stanchina[5], Jorge Reis-Filho[1,6], Neal Rosen[7], Joaquín Arribas[4], Pedram Razavi[1,2,3] & Sarat Chandarlapaty[1,2,3]✉

Inhibition of HER2 in HER2-amplified breast cancer has been remarkably successful clinically, as demonstrated by the efficacy of HER-kinase inhibitors and HER2-antibody treatments. Whilst resistance to HER2 inhibition is common in the metastatic setting, the specific programs downstream of HER2 driving resistance are not established. Through genomic profiling of 733 HER2-amplified breast cancers, we identify enrichment of somatic alterations that promote MEK/ERK signaling in metastatic tumors with shortened progression-free survival on anti-HER2 therapy. These mutations, including *NF1* loss and *ERBB2* activating mutations, are sufficient to mediate resistance to FDA-approved HER2 kinase inhibitors including tucatinib and neratinib. Moreover, resistant tumors lose AKT dependence while undergoing a dramatic sensitization to MEK/ERK inhibition. Mechanistically, this driver pathway switch is a result of MEK-dependent activation of CDK2 kinase. These results establish genetic activation of MAPK as a recurrent mechanism of anti-HER2 therapy resistance that may be effectively combated with MEK/ERK inhibitors.

# EM to examine micro-environment/BBB/BTB





Corti C et al. Cancer Treat Rev 2022

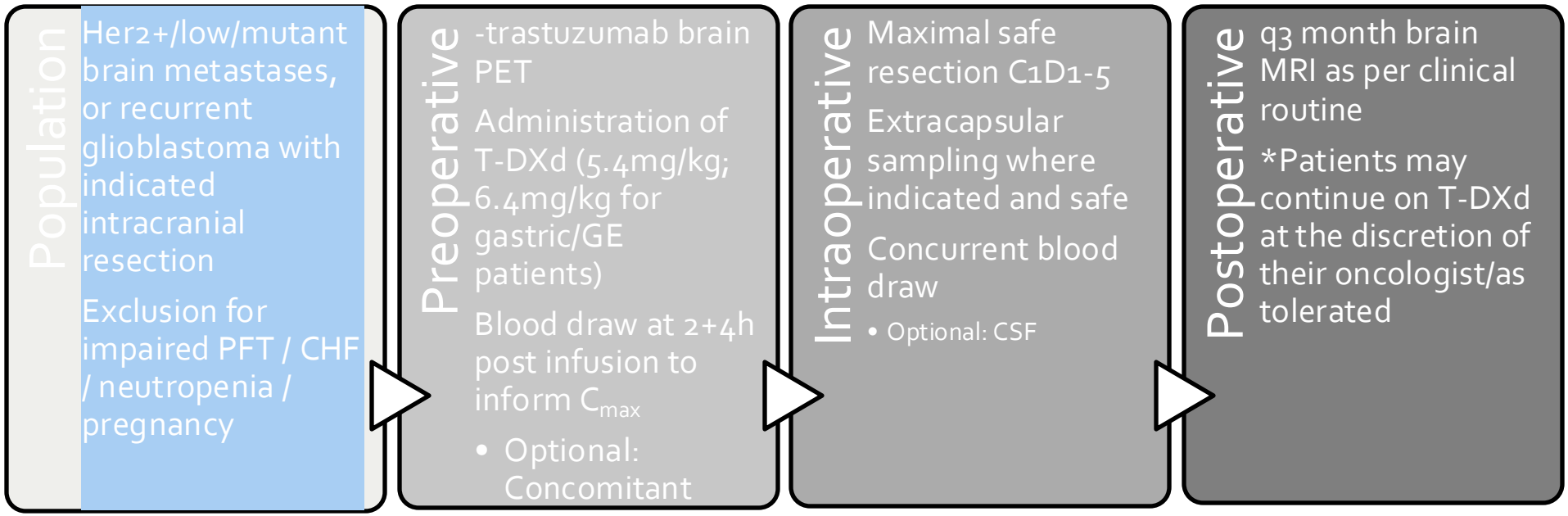
## Challenges

- Eligible patients are often highly symptomatic with need of an urgent intervention that may pose logistic hurdles
- Non-interventional nature of the study may affect the recruitment
- Available radiologic techniques do not often distinguish between radiation necrosis and actual BrM progression
- There is a technical limitation of mass spectrometry in quantifying drug concentration in viable tumor vs. necrotic tissue

## Future directions

- Continue to enroll patients, aiming for a total of 10 patients in cohort A and 10 patients in cohort B, to assess differences between tucatinib-resistant and tucatinib-naive groups.
- Enroll patients in cohort C and continue the drug post-operatively to investigate tucatinib activity in the brain for other tumor types
- As per the secondary endpoint, highlight the molecular and microenvironmental mechanisms of tucatinib resistance to inform new therapeutic strategies

# Pre-operative T-DXd WoO (WOnDER-BT)




**Cohort A**: 16 patients with Her2-expressing or solid tumors with activating ERBB2 mutations without prior T-DXd exposure
**Cohort B**: Up to 4 patients with the above diseases and prior T-DXd exposure
**Cohort C**: 4 patients with recurrent glioblastoma

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- **Dr. Nelson Moss (Neurosurgery)**
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- Dr. Elisa De Stanchina (SKI, Anti-tumor Core)
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- Verna Solomon (CRA, Breast Medicine Service)
- Megan Ramirez (CRC, Breast Medicine Service)
- Jodecy Colon (CSP)
- Lay Kaw (Pharmacy)
- Andrew Zarski (Research and Technology Mgmnt, RedCap)
- Jenny Anopa (Sr. Mgr, Study Start Up, Res&Tech Mgmnt)
- Shahiba Ogilvie (Operations Manager, Translational & Clinical Research, Neurosurgery)


Nelson Moss, MD

Emanuela Ferraro, MD

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Memorial Sloan Kettering Cancer Center


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# THANK YOU