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MANAGEMENT OF HER2+ BRAIN AND LEPTOMENINGEAL DISEASE

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DISCLOSURES

Contracted Research	AbbVie Inc, Astellas Pharma Global Development Inc, Medivation Inc, a Pfizer Company, Merrimack Pharmaceuticals Inc, Novartis, Pfizer Inc

Case presentation: Dr Brooks

69-year-old morbidly obese woman (350 pounds) with a history of DM

- 2016: Metastatic ER/PR-negative, HER2-positive BC: 8-cm breast mass, 5-cm axillary mass, 3 liver lesions (9 cm, 7 cm and 2.5 cm) and 2 small lung lesions
  - Trastuzumab/pertuzumab/paclitaxel x 2 cycles
    - Mucositis, oral candida, diarrhea
    - Decreased paclitaxel dose - hypersensitivity reaction
  - *Nab* paclitaxel at 30% dose reduction → oral candida, umbilical candida, diarrhea, tachycardia
  - Currently on pertuzumab/trastuzumab and faring well

Case presentation: Dr Hart

58-year-old woman

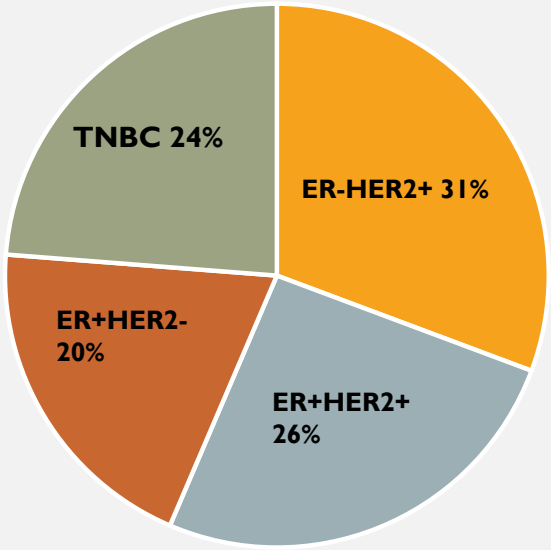
- 2011: Metastatic ER/PR-positive, HER2-positive BC with symptomatic brain mets → surgical resection of brain lesion → XRT to brain → chemotherapy/trastuzumab → trastuzumab + AI
- 2016: Lapatinib + capecitabine
  - Further resection of cerebellar lesions
- 2017: Fulvestrant + lapatinib + capecitabine
- Currently on fulvestrant + palbociclib + trastuzumab

ROADMAP

- Incidence
- Guidelines for management
- Systemic therapy
- New directions

BRAIN METASTASES IN BREAST CANCER

- Brain metastases common in breast cancer
- Incidence and outcome varies with different breast cancer subtypes



Brain Met Distribution
n = 400

Median Survival

ER-HER2+ 17.9 months

ER+HER2+ 20.7 months

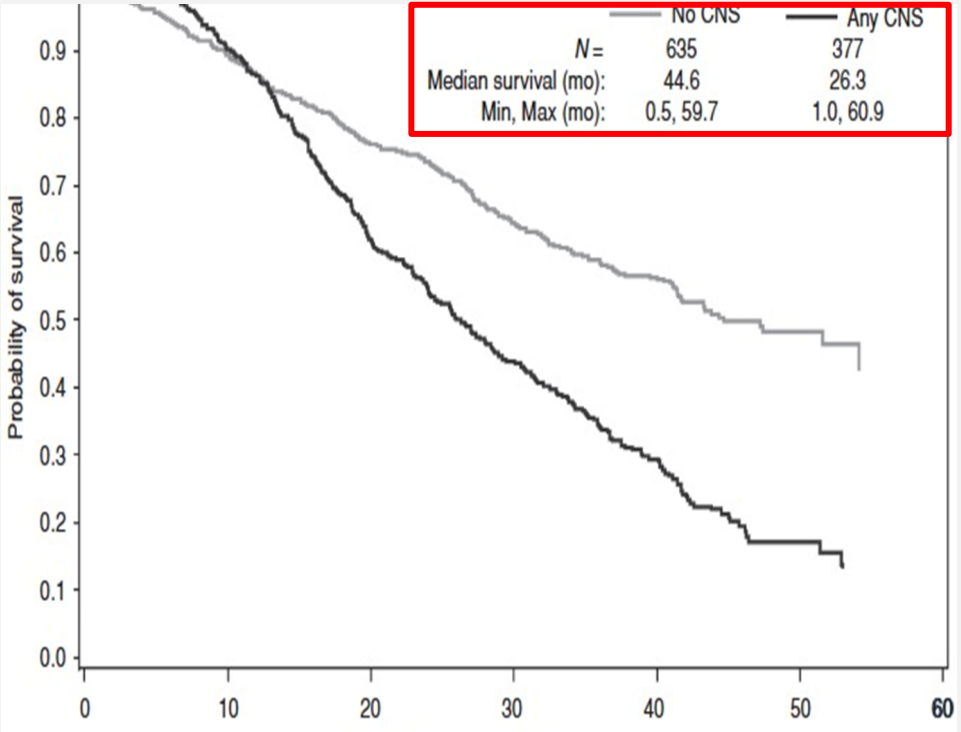
ER+HER2- 9.7 months

TNBC 6.4 months

Sperduto, Int J Radiat Oncol Biol Phys. 2013

HER2+ BRAIN METS: NATURAL HISTORY

- registHER examined the natural history of patients with newly diagnosed HER2+ MBC
  - From 2003-2006
- 37% of patients with HER2+ MBC had brain mets detected over the study
  - 7% at diagnosis
  - 30% over the course of their disease
- Worse outcome with presence of brain mets
  - Median survival 26.3 months with vs. 44.6 months without



Brufsky, Clin Cancer Res, 2011

HER2 BRAIN METASTASES

Study	Treatment	Overall Outcome	CNS Metastases Outcome
CLEOPATRA	THP vs. TH	THP> TH	↓ Development CNS mets with THP
EMILIA	T-DM1 vs. Capecitabine/Lapatinib	T-DM1> Cape/Lapatinb	↑ OS with T-DM1 in pts with CNS mets
TH3RESA	T-DM1 vs. Physicians choice	T-DM1 > TPC	↑ PFS with T-DM1 in pts with CNS mets
CEREBEL prevention	Lap/cape vs. Tras/cape	Tras/cape > Lap/Cape	No diff. in development of CNS mets Tras/cape- 5% Lap/cape- 3%

Dawood Ann Oncol 2008; Swain Ann Oncol 2014; Krop Ann Oncol 2015, Krop Lancet Oncol 2014, Pivot J Clin Oncol 2015

INITIAL CNS DISEASE ASCO GUIDELINES

- Favorable prognosis with single or limited (≤ 4 lesions)
  - Surgery with postoperative radiation, stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT; SRS), depending on metastasis size, resectability, and symptoms.
- Diffuse disease/extensive metastases or symptomatic leptomeningeal
  - WBRT
- Poor prognosis
  - WBRT
  - Palliative care

Ramakrishna et al, JCO 32:2100-08, 2014

PROGRESSIVE CNS DISEASE ASCO GUIDELINES

- Options vary based on initial treatment, location, symptoms
  - SRS
  - Surgery
  - WBRT
  - systemic therapy
  - clinical trial

Ramakrishna et al, JCO 32:2100-08, 2014

SYSTEMIC THERAPY ASCO GUIDELINES

- If NO systemic progression
  - DO NOT CHANGE SYSTEMIC THERAPY
- If systemic disease is progressing
  - Follow treatment algorithm for systemic disease
- To put that another way…..CNS disease should NOT impact systemic management

Ramakrishna et al, JCO 32:2100-08, 2014

Lapatinib

Study	Regimen	N	Prior chemo	Prior RT	Response criteria	CNS ORR	TTP/ PFS	OS
Lin et al CCR 2009*	L + cape	50	81% with ≥2 T+chemo; PD on lapatinib monotherapy	100%	50% vol NSS, steroids, lack of non-CNS PD	**20%**	3.6 mo	NR
Boccardo et al, ASCO 2008 (LEAP)	L + cape	138	Prior T required	NR	Investigator-assessed on survey	**18%**	Median time on study 2.8 mo	NR
Sutherland et al, Br J Ca 2010 (LEAP)	L + cape	34	82% with ≥2 chemo for MBC; prior T required	94%	RECIST	**21%**	5.1 mo	NR
Metro et al, Ann Oncol 2011	L + cape	22	Median of 2 prior T-based tx for MBC	86%	WHO	**32%**	5.1 mo	27.9 mo
Lin et al, 2011 *submitted**	L + cape	13	Prior T required	100%	50% vol, NSS, steroids, lack of non-CNS PD	**38%**	NR	NR
Bachelot et al, ASCO 2011*	L + cape	45	**22% with ≥2 T+chemo (31%: no prior T for MBC)**	0%	50% vol, NSS, steroids, lack of non-CNS PD	**67%**	**5.5 mo**	91% alive at 6 mo

L: lapatinib; cape: capecitabine; T: trastuzumab; NR: not reported

* Prospective trial

NERATINIB

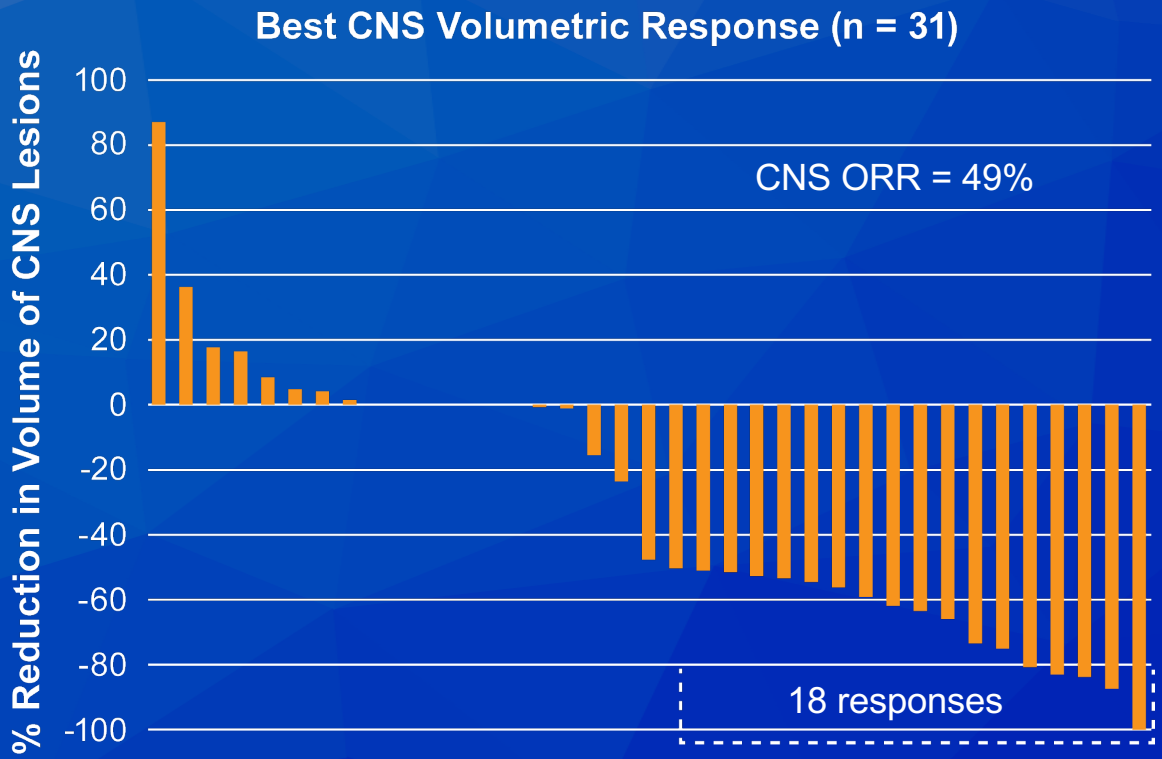
- N=40
- 78% prior WBRT
- 3 partial responses (ORR 8%)
- Median PFS 1.9 months
- Quality of life decreased over time

Freedman et al, JCO 20;34(9):945-52, 2016 (TBCRC 022)

TBCRC 022: Phase II trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2 (HER2+) breast cancer brain metastases (BCBM)

Freedman R et al.
Proc ASCO 2017;Abstract 1005.

Primary Endpoint: CNS Volumetric Response



- Median overall survival: 13.5 mo
- Most frequent Grade 3 toxicity: Diarrhea (24% on prior pertuzumab, 44% without prior pertuzumab)

Freedman R et al. *Proc ASCO* 2017;Abstract 1005.

PHASE I TRIAL OF ONT-380 + T-DM1

ONT-380

- Highly selective for HER2 (IC_{50} 8 nM) over EGFR (IC_{50} >10,000 nM)
- Decreased potential for EGFR-related toxicities (e.g. diarrhea)

Treatment

- 50 patients treated with:
  - ONT-380 at RP2D 300 mg BID plus
  - T-DM1 3.6 mg/kg IV q21 days

Patient Population

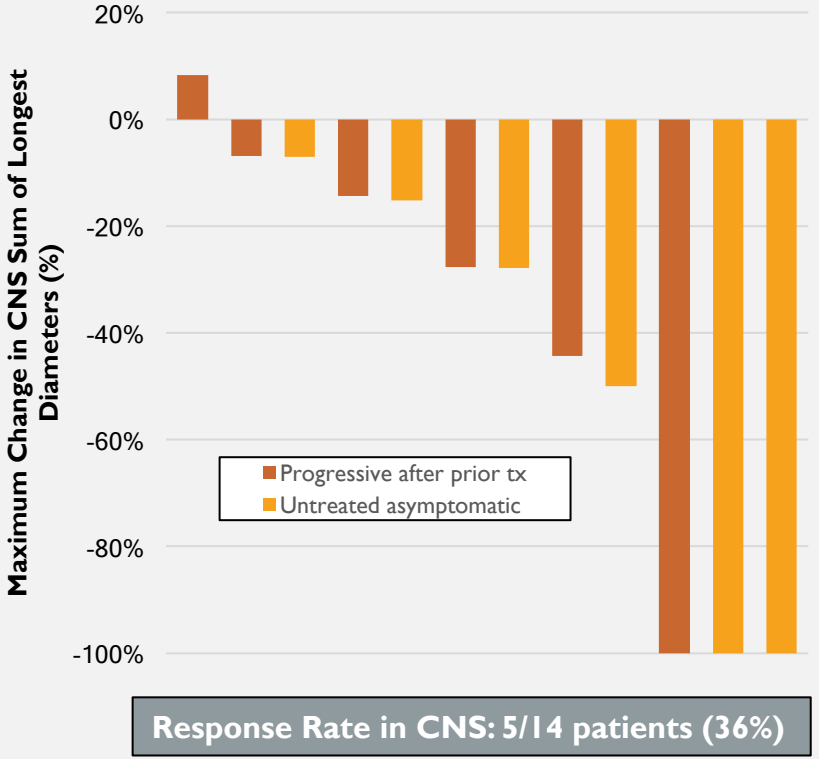
- HER2+ MBC with progression after prior therapy with trastuzumab and a taxane, no prior T-DM1
- Patients with brain metastases eligible, including untreated metastases or metastases progressive after prior treatment

	Patients Treated (n = 50)
Age, median (range)	51 (30-72)
ECOG 0/1, n (%)	20 (40%)/30 (60%)
Hormone receptor positive, n (%)	34 (68%)
Time since metastatic diagnosis (mos), median (range)	20 (1-93)
Prior HER2 agents, median (range)	**2 (1-3)**
Trastuzumab, n (%)	50 (100%)
Pertuzumab, n (%)	23 (46%)
Lapatinib, n (%)	10 (20%)
Brain Mets, n (%)	**30 (60%)**
Stable, treated brain mets, n (%)	9 (18%)
Untreated or progressing mets, n (%)	21 (42%)

Borges et al, ASCO 2015, abstract 513

BRAIN METASTASES OUTCOMES

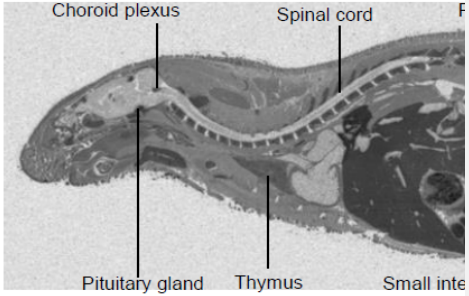
- 20 pts w/o brain mets at baseline
  - None developed brain mets
- 30 patients with brain mets at baseline:
  - 36% CNS specific RR
  - Brain met TTP=8 mo.
  - 15 pts had brain progression
  - 4 pts had systemic progression



Borges et al, ASCO 2015, abstract 513

TESEVATINIB + TRASTUZUMAB

- **Tesevatinib (KD019)**
  - Small molecule TKI
  - Targets EGFR, HER2, VEGFR2/3, and Src
  - **Preclinically crosses intact BBB**
- **Patient Population:**
  - HER2+ MBC with disease progression, with or without brain metastases
  - Prior trastuzumab, pertuzumab, T-DM1
  - Heavily pre-treated median prior therapies 6-11 on all dose levels
  - n= 17; 4 pts with brain metastases
- **4 patients had known brain metastasis at study entry:**
  - 3/4 did not progress in their CNS disease while on tesevatinib therapy
  - One patient had objective response in 2 brain lesions (12 mm to 4 mm; 13 mm to 4 mm) with other brain lesions stable; progressive CNS disease after 10 cycles



Quantitative Whole Body Autoradiography (QWBA) following a single oral administration of [14C]-Tesevatinib to male partially pigmented rats

Tonra, AACR 2015

Lin et al, ASCO 2015, abstract 514

ONGOING CLINICAL TRIALS

- Intrathecal trastuzumab and pertuzumab
- T-DM1 + low dose temozolomide (post SRS)
- RT +/- lapatinib (NRG)
- Palbociclib + trastuzumab
- Nal-IRI (MM-398)
- Selective intra-arterial infusion of trastuzumab
- Cabozantinib + trastuzumab
- Capecitabine + trastuzumab +/- tucatinib