Phase II trial of Neratinib and Capecitabine for Patients with Human Epidermal Growth Factor Receptor 2-Positive (HER2+) Breast Cancer Brain Metastases

Translational Breast Cancer Research Consortium (TBCRC) 022

NCT01494662 **Abstract #1005**

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tbcrc Translational Breast Cancer Research Consortium

Background

- Up to half of patients with metastatic HER2+ breast cancer will develop brain metastases
- Evidence-based treatments for CNS disease are limited, particularly when progression occurs after local therapy (e.g. SRS, WBRT, surgery)
- Recurrent CNS events remain a major source of patient morbidity and mortality

Lin, NU J Clin Oncol, 2004; Eichler AF, et al. Cancer, 2008; Gori S, et al Oncologist, 2007; Melisko ME J Neurooncol, 2008; Olson EM, et al. Breast, 2013; Pestalozzi BC et al Lancet Oncol 2013 (HERA trial data)

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Neratinib

- Potent, oral, irreversible-binding inhibitor of the erbB family of receptor tyrosine kinases
  - Inhibits signal transduction through EGFR, HER2, HER4
- Active in *extra-cranial* disease as monotherapy[1]
  - Objective response rate = 24% (prior trastuzumab-treated)
  - Objective response rate = 56% (no prior trastuzumab)
- Active systemically when combined with chemotherapy[2-6]
- Activity in CNS not well established but preclinical data suggest penetration

[1]Burstein et al. J Clin Oncol, 2010; [2]Awada A et al JAMA Oncol 2016; [3]Chow LW et al Br J Cancer 2013, [4]Awada A et al. Ann Oncol 2013; [5]Saura C et al, J Clin Oncol, 2014; [6] Awada A et al JAMA Oncol 2016

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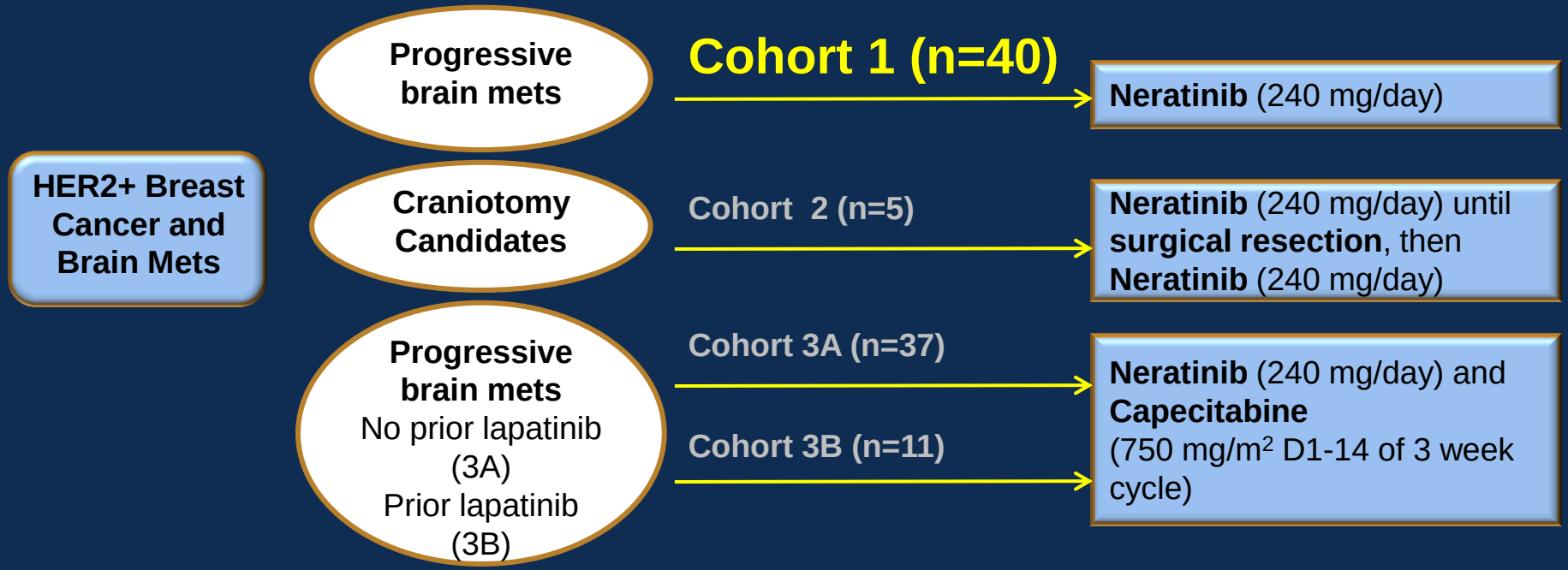
TBCRC 022 Study Cohorts

****All cohorts now closed to enrollment****



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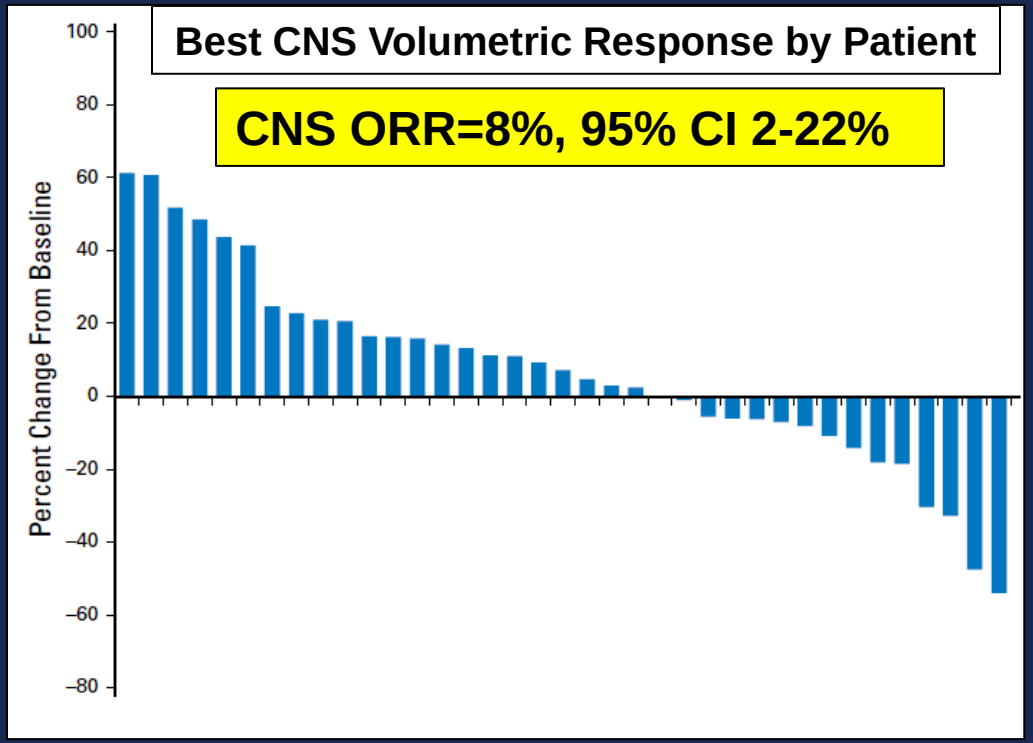
TBCRC 022 Cohort 1: Neratinib Monotherapy

CNS volumetric responses observed but did not meet pre-specified threshold to prompt further investigation as monotherapy



Freedman et al. J Clin Oncol 2016; Table/Figure re-used with permission. © (2017) ASCO. All rights reserved.

TBCRC 022 Study Cohorts

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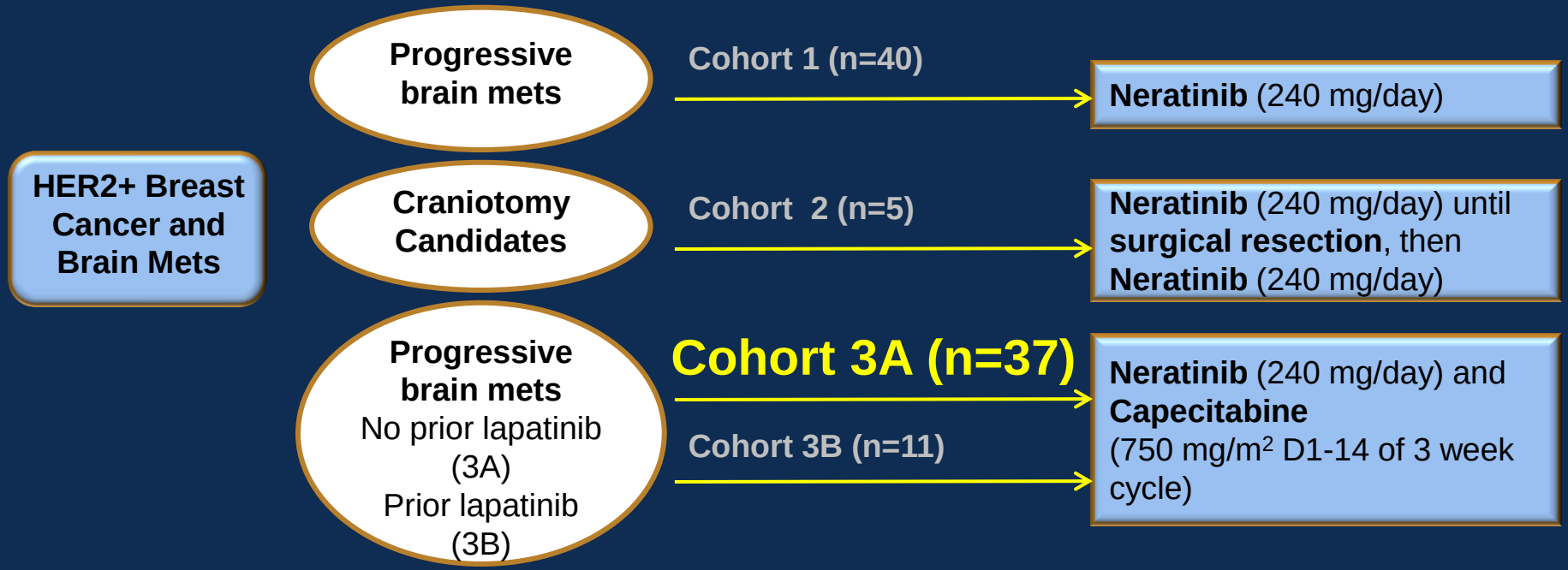

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Capecitabine is an Appealing Partner for Neratinib

Trial	Response Rate
CNS setting	
LANDSCAPE[1] –CNS tx- naïve Lapatinib + capecitabine	CNS Volumetric ORR = 67%
EGF105084[2]– Prior CNS tx, prior lapatinib Lapatinib + capecitabine	CNS Volumetric ORR = 20%
Capecitabine + temozolomide[3] –Tx-naïve & prior tx	CNS Volumetric ORR = 18%
Non-CNS setting	
Neratinib + capecitabine[4]	Extra-CNS ORR = 64%
NALA – neratinib + capecitabine vs. lapatinib + capecitabine (no active CNS disease)	Enrolling

[1]Bachelot T, et al Lancet Oncol, 2013; [2]Lin N.U., et al CCR, 2009; [3]Rivera E et al Cancer 2006; [4]Saura C et al, J Clin Oncol, 2014

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Key Study Eligibility

Inclusion Criteria

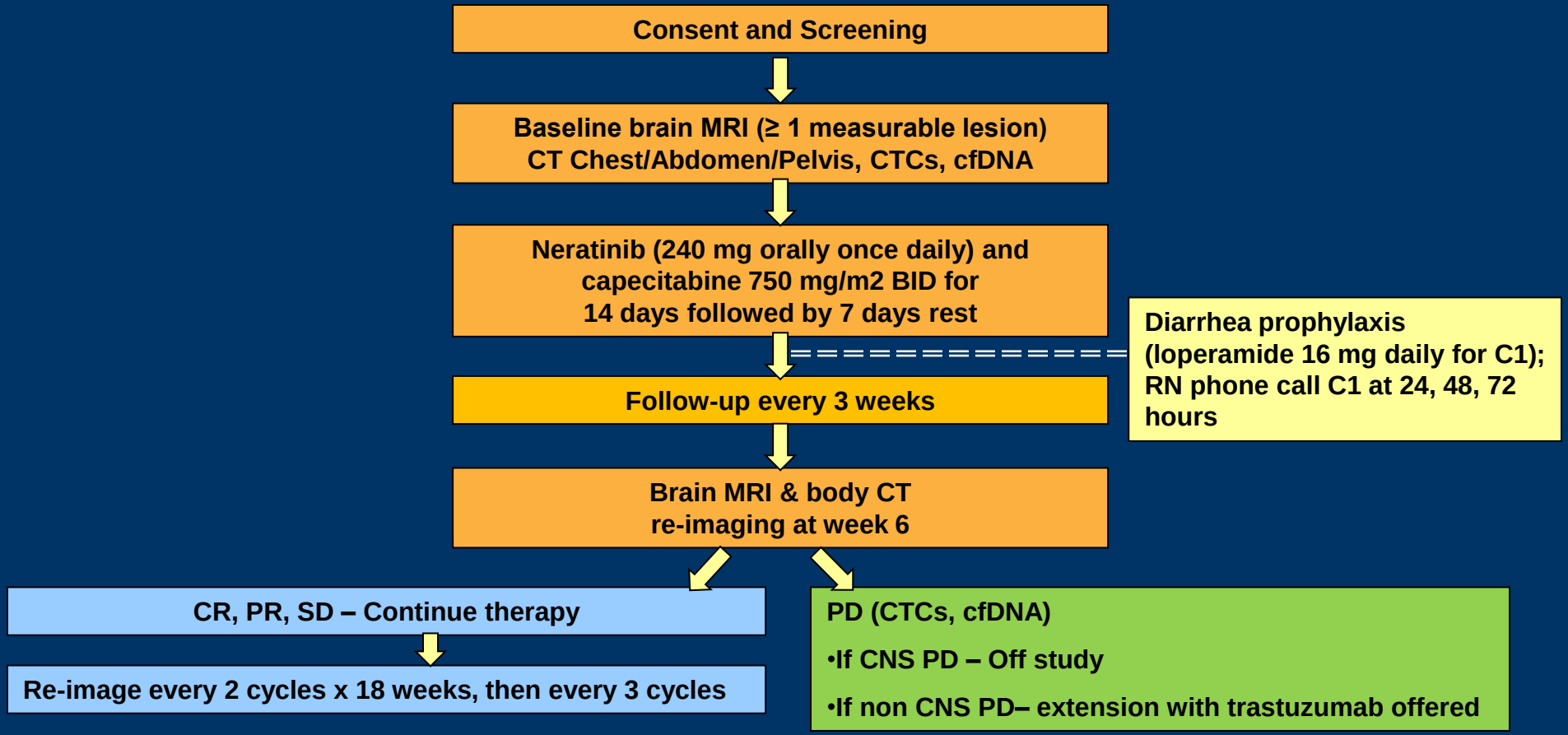
- HER2+ metastatic breast cancer[1]
- CNS progression (new or previously treated site) after ≥1 line of local CNS therapy
- Measurable disease: ≥ 1 CNS lesion ≥ 10 mm
- ECOG PS 0-2
- Adequate end-organ function
- Normal ejection fraction

Exclusion Criteria

- Prior capecitabine
- Prior lapatinib
- Leptomeningeal disease only
- Significant malabsorption or diarrhea syndrome
- Active escalation of steroids

[1] Wolff AC et al J Clin Oncol 2013

Study Design



Study Endpoints

- **Primary**
  - CNS Objective Response Rate (ORR) according to composite (volumetric) criteria
- **Secondary**
  - CNS response by Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) Criteria[1]
  - Progression-free and overall survival
  - Site of first progression
  - Toxicity
- **Correlative (forthcoming)**
  - Molecular CTC studies for correlation with response and survival
  - cfDNA at baseline and at therapy discontinuation
  - Tissue, CSF, blood collections on cohort 2 patients for neratinib concentrations

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[1] Lin NU, et al. Lancet Oncology, 2015

Requirements for Partial Response

Qualifying Criteria	*Primary Endpoint*	*Secondary Endpoint*
	Composite Criteria	**RANO-BM Criteria**
Brain lesions		
Target	**≥ 50% ↓ volume**	**≥30% ↓ sum longest diameter (LD) (w/ confirmation ≥4 weeks later)**
Non-target	None / CR	None / no progression
New	None	
Steroids	Stable or ↓	
Clinical status	Stable or improving neurological signs and symptoms	Stable or improving clinical status
Systemic disease (RECIST)	No progression	Calculated separately

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Statistical Considerations – 1° Endpoint

- CNS volumetric ORR assessed by central review at Tumor Imaging Metrics Core (Boston, MA) and by local evaluation of non-CNS imaging (RECIST 1.1), neurologic symptoms, steroid dosing

- Simon two stage design **[H_o=15%, H_A=35%]**
  - If ≥ 5/19 respond→ enroll 16 additional pts [achieved]

- Worthy of further study if ≥ 9/35 respond (ORR ≥ 26%)
  - To assess whether the CNS ORR of the combination is more promising than anticipated (historical) ORR for capecitabine alone

Probability of…	If true CNS ORR=15%	If true CNS ORR=35%
stopping trial early	0.86	0.15
deeming worthy of further study	0.05	0.80

Study Status

- Enrolled during 4/22/14 – 11/16/16
- 11 TBCRC sites
- 37 patients initiated protocol therapy
  - Median # of initiated cycles = 6 (range 1-30)
    - 7 patients (19%) received 10+ cycles
  - 3 patients remain on therapy as of 4/1/17
    - On cycles 25, 8, 9
- Results based on all data available as of 4/1/17

Enrolling TBCRC Sites
Dana-Farber/Harvard Cancer Center
Johns Hopkins
UCSF
Baylor
U Michigan
Duke
UPMC
Mayo
MD Anderson
UNC
Georgetown

Patient Characteristics (n=37)

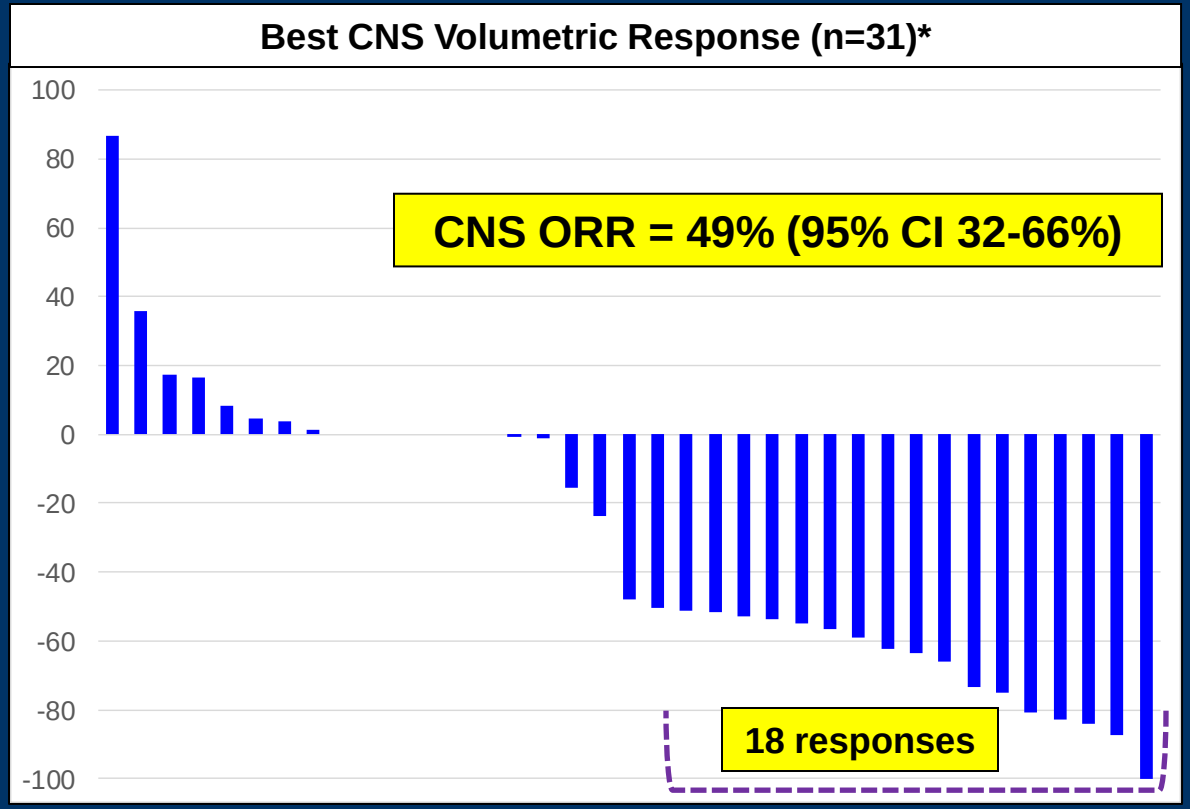
Baseline Patient Characteristic	*N (%)*
Age (years)	Median = 53 (range 31-64)
Race	
White	32 (86)
Asian	2 (5)
Black	1 (3)
More than 1 race/other	2 (5)
Primary tumor ER status	
Negative (incl. 1 borderline)	21 (57)
Positive	16 (43)
ECOG PS	
0	13 (35)
1	20 (54)
2	4 (11)
Sites of disease (not mutually exclusive)	
CNS parenchymal disease	37 (100)
Leptomeningeal disease	2 (5)
Lung	9 (24)
Liver	10 (27)
Bone	21 (57)
Breast or chest wall	6 (16)
Lymph nodes	6 (16)
Number of sites of disease (outside CNS)	Median = 1 (range 0-4)

Patient Characteristics, cont.

Baseline Patient Characteristic	*N (%)*
Number of prior chemotherapy agents* (metastatic setting)	Median = 1 (range 0-3)
Systemic Treatment (metastatic setting)	
Trastuzumab	33 (89)
Taxane	25 (68)
Pertuzumab	21 (57)
Trastuzumab emtansine	8 (22)
Vinorelbine	4 (11)
Other Investigational HER2-directed agents	5 (14)
Platinum	1 (3)
Eribulin	1 (3)
Past Local CNS Treatments	
Surgery	11 (30)
SRS	12 (32)
WBRT	24 (65)
≥ 2 prior local CNS treatments	13 (35)
No prior CNS treatment	3 (8)

*Does not include hormonal therapy, antibodies alone, everolimus, or targeted HER2 agents

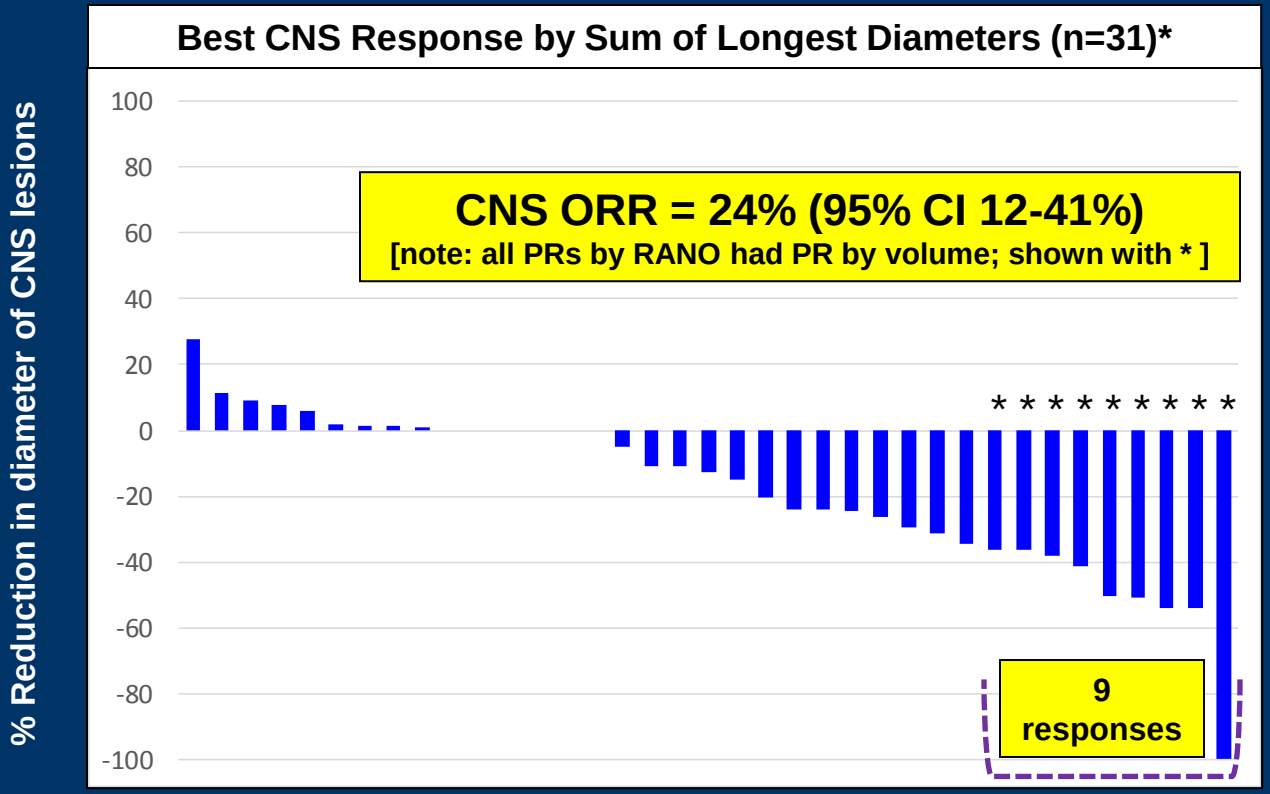
Primary Endpoint – CNS Volumetric Response



* 6 patients did not reach first re-staging evaluation and are categorized as '0'

┼ No patient had clear increase in steroid use, non-target lesions, non-CNS lesions, or worsening neurological symptoms at time of radiographic response

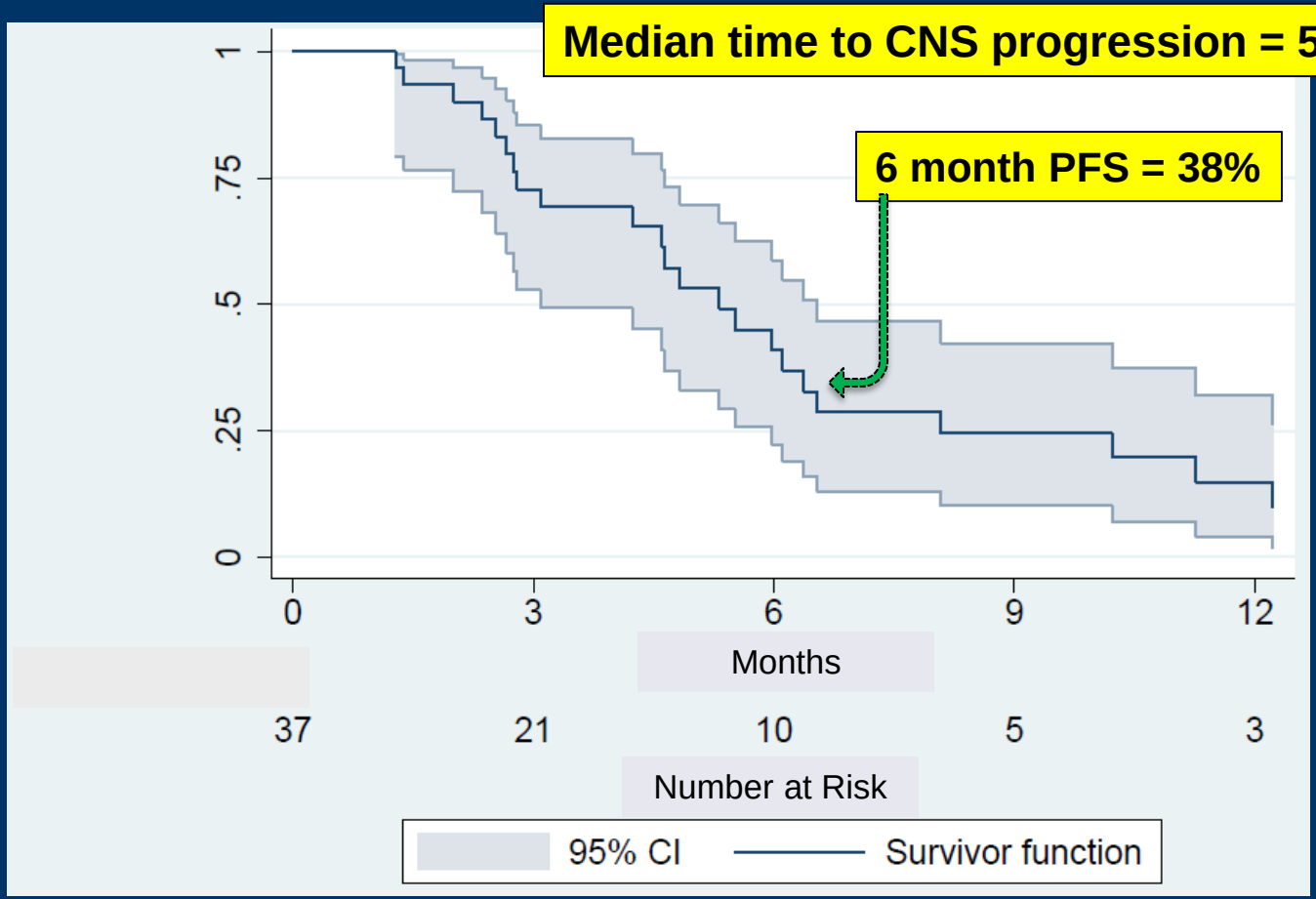
Secondary Endpoint— CNS ORR by RANO-BM*



[+ 2 additional unconfirmed responses]

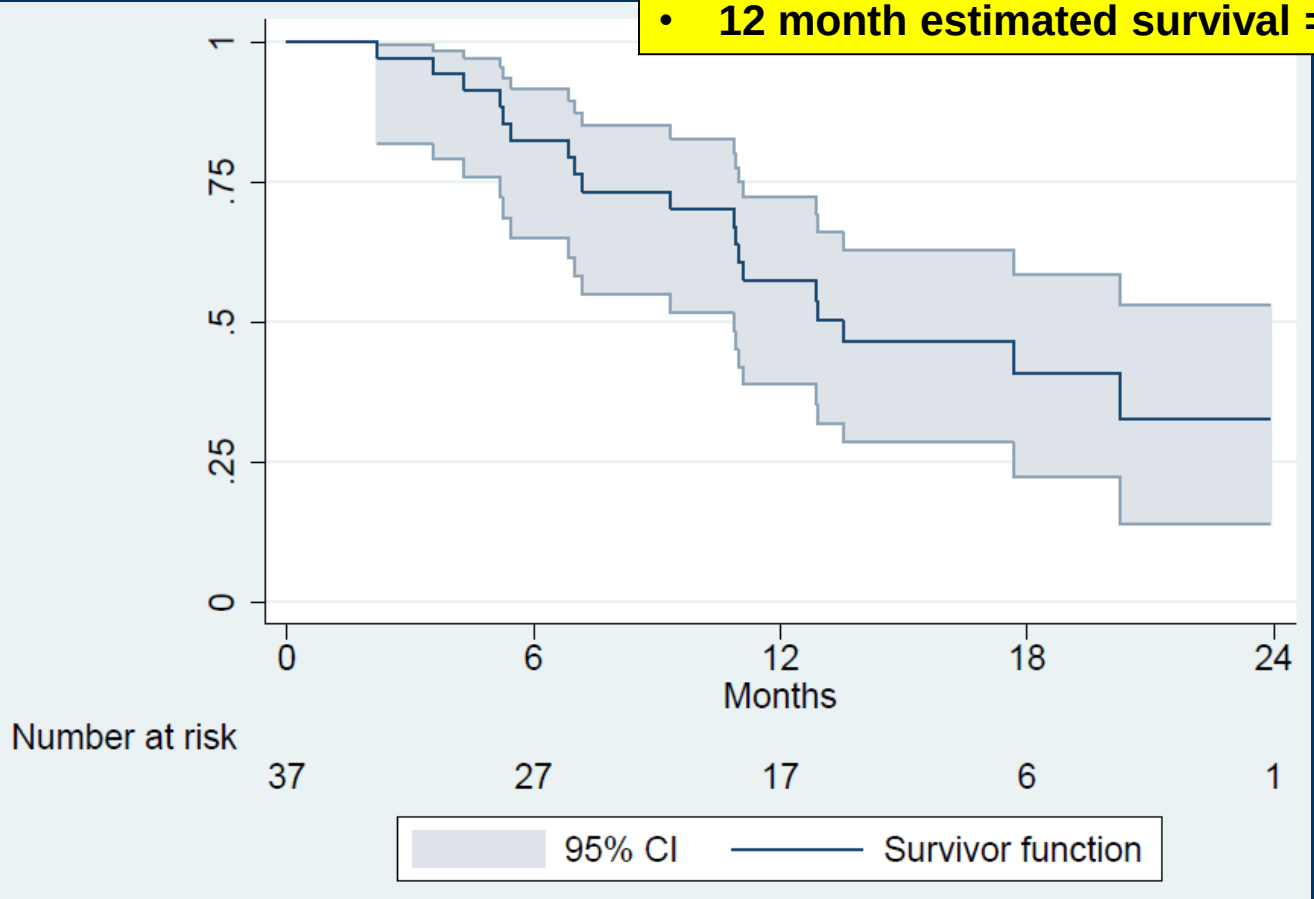
* 6 patients did reach first re-staging and are categorized as '0'
┼ No patient had equivocal increase in steroid use, non-target lesions, non-CNS lesions, or worsening neurological symptoms at time of radiographic response

Time to CNS Progression

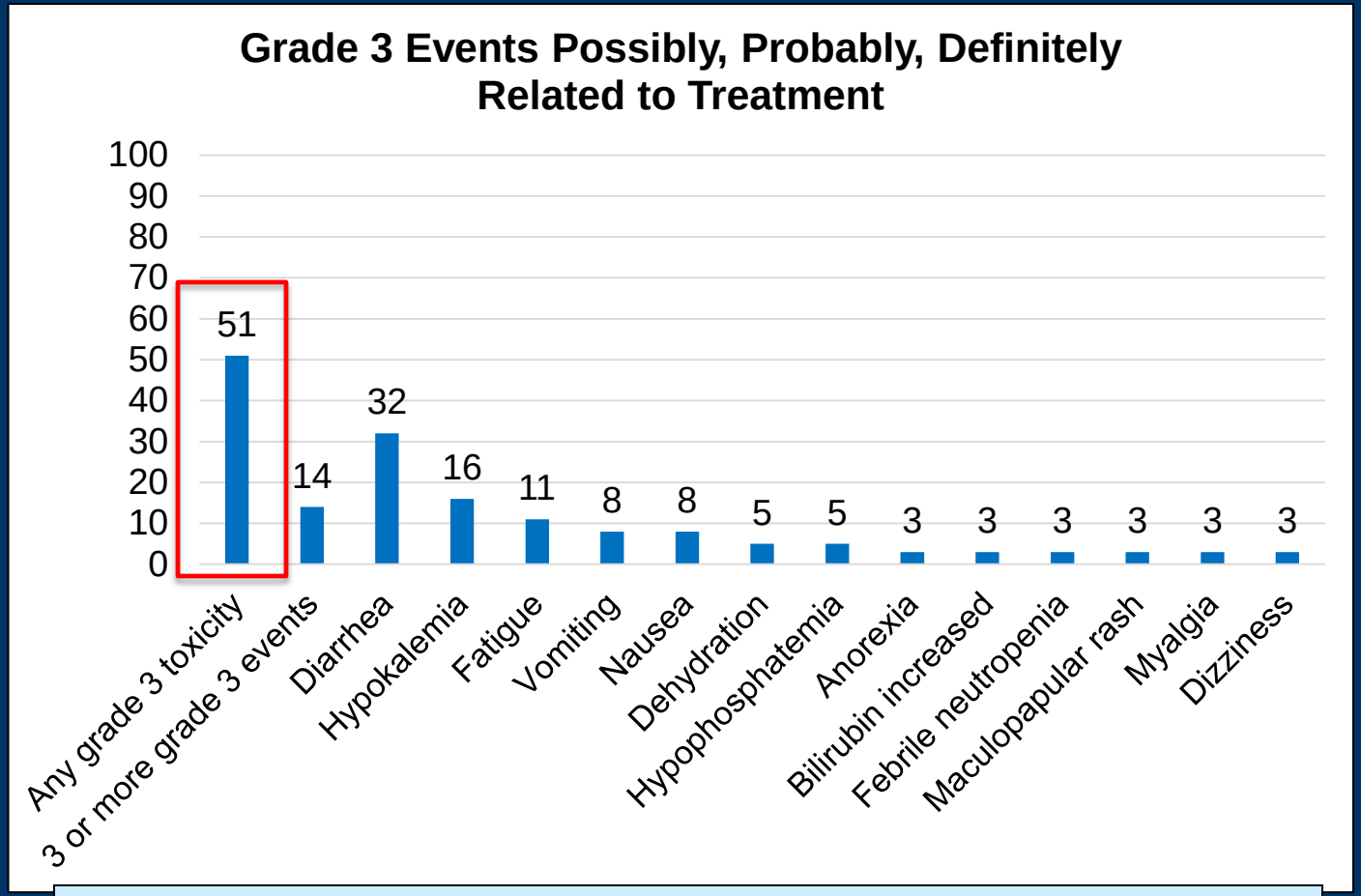


Overall Survival

- **Median OS = 13.5 months (19 events)**
- **12 month estimated survival = 57% (95% CI 39-72%)**



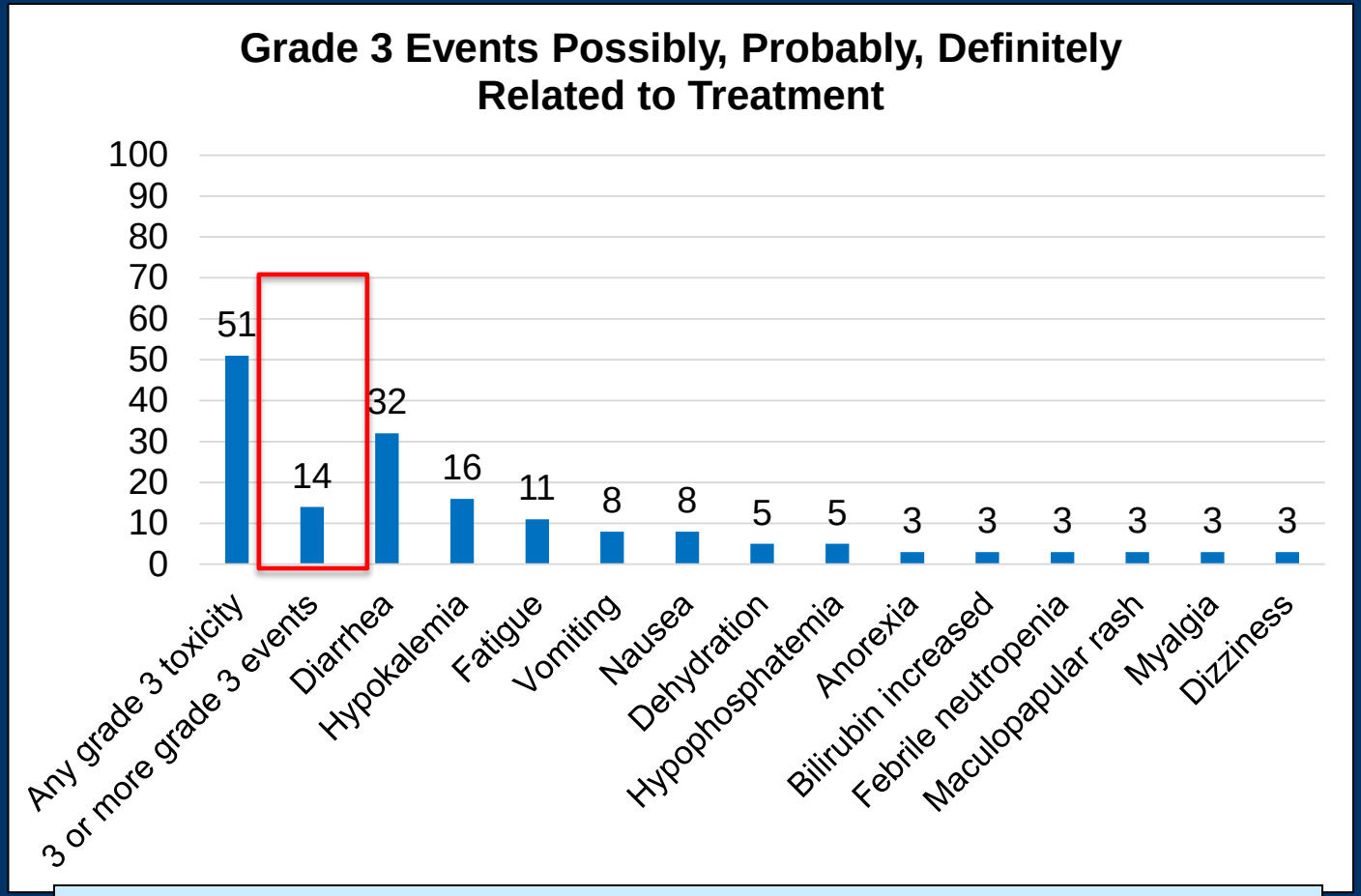
Toxicity*



*No grade 4-5 treatment-related events

*5/21 with prior pertuzumab had grade 3 diarrhea (24%)
*7/16 without prior pertuzumab had diarrhea (44%) [2 sided Fisher exact p-value=0.29]

Toxicity*



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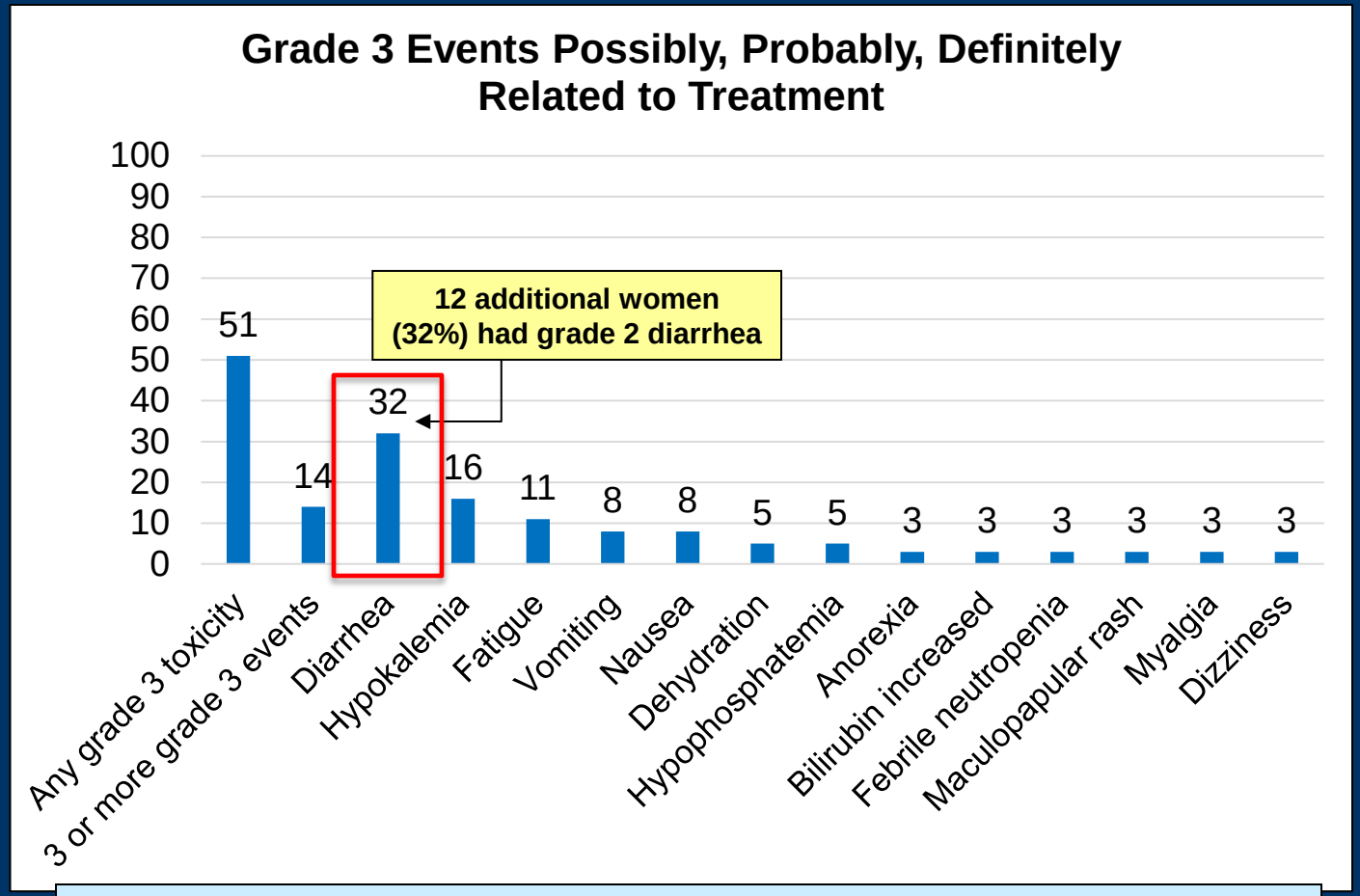

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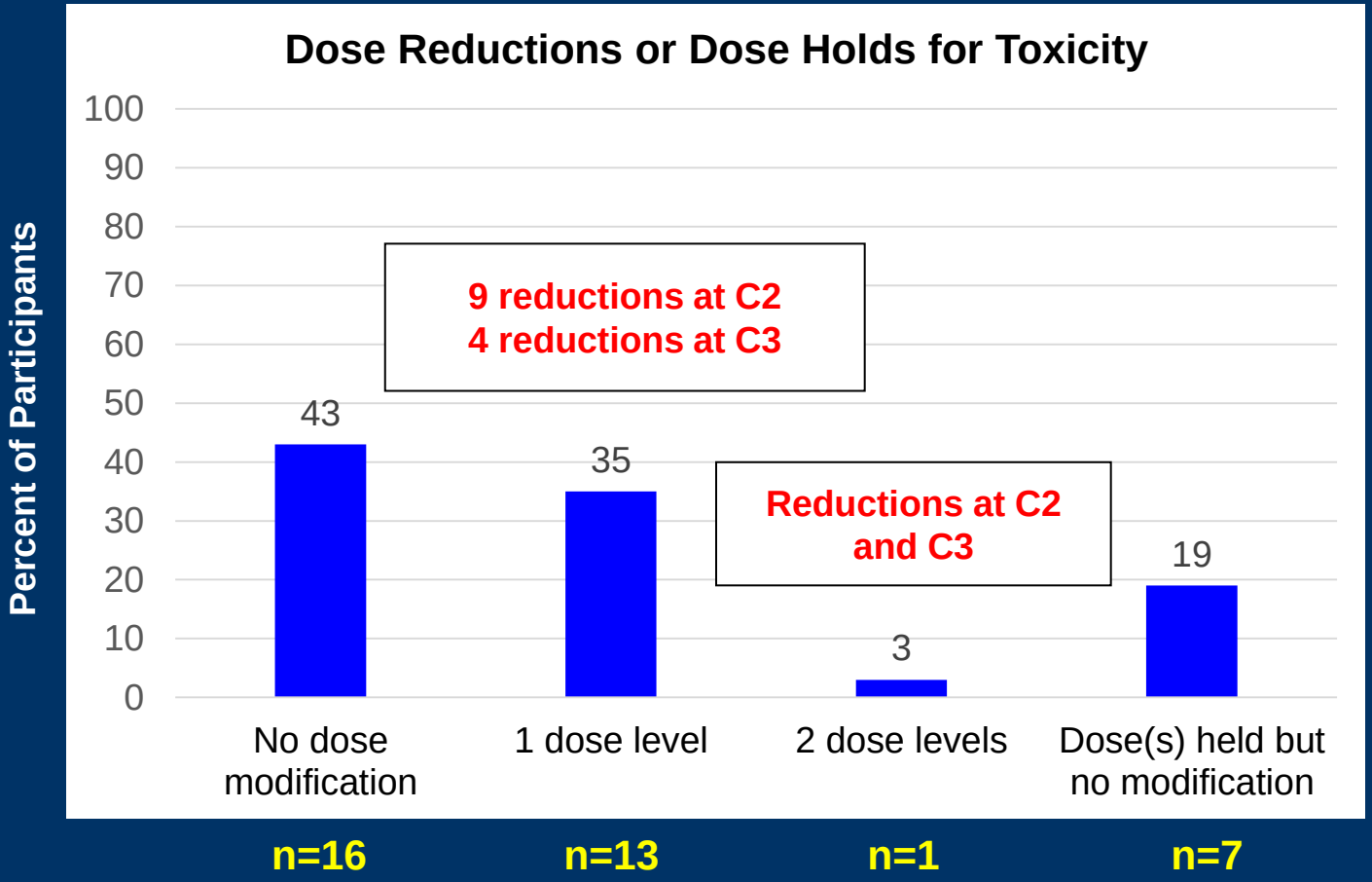
Dose Modifications



Reasons for Cessation of Study Therapy

Reason off study	N (%)
CNS progression*	20 (54)
CNS and non-CNS progression	3 (8)
Unacceptable toxicity	7 (19)
Physician discretion	2 (5)
Patient withdrawal	2 (5)
Still on study treatment as of April 1, 2017	3 (8)

*including those with symptomatic deterioration and not radiographic progression

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Study Conclusions

Neratinib plus capecitabine is an active treatment combination for HER2+ disease metastatic to the CNS in pre-treated patients

- 49% CNS ORR by composite criteria
- 24% CNS ORR by RANO-BM criteria
- Median time to CNS progression = 5.5 months
- Prolonged disease control was seen in many:
  - 51% initiated 6+ cycles of therapy, 19% initiated 10+ cycles
- Although our observed median OS of 13.5 months is similar to that reported in past studies[1,2], 49% study patients remain alive as of April 1, 2017

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[1] Cortes et al Lancet Oncology (LUX-Breast 3) 2015,
[2] Eichler AF, et al. Cancer, 2008

Study Implications and Next Steps (1)

- Multicenter trials for this patient population are feasible and indicative of a significant unmet medical need (95 patients enrolled to cohorts 1-3)

- Our results provide further support for the efficacy of HER2-directed systemic therapy for the treatment of breast cancer brain metastases

- Future studies could examine local therapy vs. systemic therapy in CNS disease and further explore the role neratinib-based combination regimens

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Study Implications and Next Steps (2)

- Further efforts to optimize toxicity management with neratinib-based regimens will be required to reduce the impact on QOL
  - Alternatives to loperamide are being explored

- Correlative studies in CSF/plasma/tissue, cell-free DNA, and CTCs are forthcoming and we will hope will further inform results

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Special Thanks to …

AVON Foundation for Women

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… for their support of the TBCRC

…And all of the enrolled patients and their families…

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Additional Acknowledgements

- Mentorship and Study Design: Nancy Lin, Eric Winer, TBCRC HER2 working group, Antonio Wolff, TBCRC
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- Statistics: Rebecca Gelman
- Data and protocol management: Christine Cotter, Sarah Farooq, Anne Cropp, Nicole Ryabin
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- Collaboration: all TBCRC co-investigators, including additional co-authors Mothaffar Rimawi, Paula Pohlmann, and Nuhad Ibrahim

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Extra Slides - Preclinical Data

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Neratinib and the CNS

- Activity in CNS not well established but preclinical data suggest penetration
  - Recent, preliminary evidence of inhibition of phosphorylated HER2 in intracranial PDX model of HER2+ breast cancer brain metastases (unpublished data, Zhao laboratory)
- Incidence of brain metastases lower on NEfERT-T trial in those treated with neratinib:
  - Neratinib-paclitaxel (10% incidence of brain mets on study at 24 months)
  - Trastuzumab-paclitaxel (vs. 20%; OR=0.45, p=.004)
  - Time to CNS metastases was delayed in neratinib-treated patients

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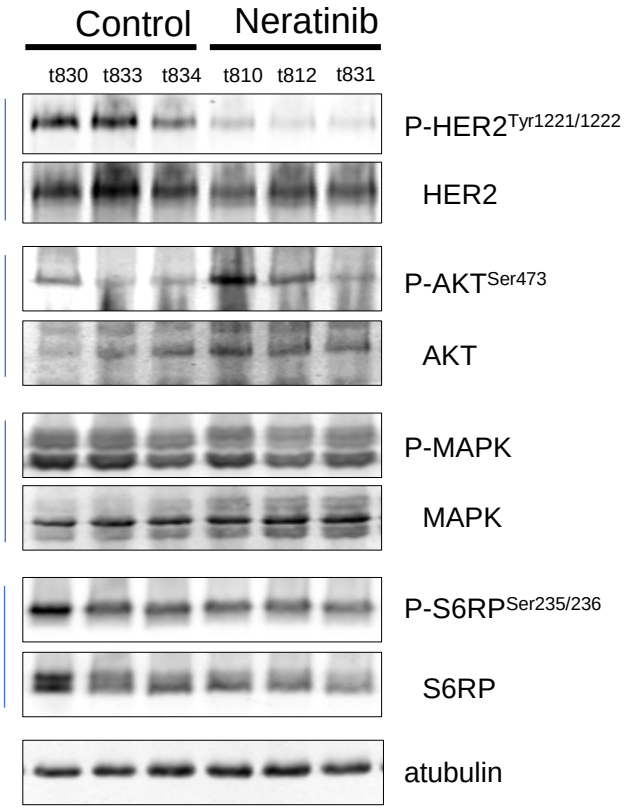
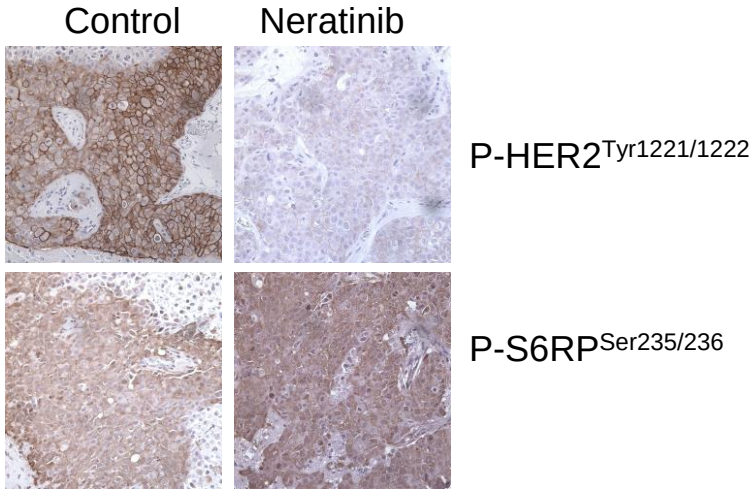
Awada A et al. NEfERT-T trial, JAMA Oncology, 2016

DF-BM355





The mice bearing orthotoptic HER2+ BCBM PDX (DF-BM355) were daily treated with Neratinib 80mg/kg for 4 days. Two hours after last dosing, the tumors were collected and subjected to Western blot analysis and IHC.

Jing Ni, Zhao Lab, Unpublished