Neratinib and ado-Trastuzumab-Emtansine (T-DM1) for HER2+ Breast Cancer Brain Metastases (BCBM): Translational Breast Cancer Research Consortium (TBCRC) Trial 022

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Background

- Treatments are limited for patients (pts) with HER2+ BCBM
- We previously reported a volumetric central nervous (CNS) system objective response (ORR) of 8% with neratinib monotherapy (Cohort 1), and 49% with neratinib plus capecitabine in lapatinib-naïve pts (Cohort 3)
- Preclinical data suggest that neratinib may overcome resistance to T-DM1 and that the combination has potential CNS efficacy.
- Here, we report results of neratinib plus T-DM1 in pts with HER2+ BCBM in Cohorts 4A, 4B, and 4C of TBCRC 022

Patients and Methods – Cohorts 4A,4B,4C

- TBCRC 022 is a prospective, multicenter, phase II study
- Pts with measurable HER2+ BCBM received neratinib 160 mg orally once daily plus T-DM1 3.6 mg/kg IV every 21 days in three parallel-enrolling cohorts.
- Cohort 4A → pts with previously untreated BCBM
- Cohort 4B → pts with BCBM progressing after prior local CNS-directed therapy *without prior T-DM1 exposure*
- Cohort 4C → pts with BCBM progressing after prior local CNS-directed therapy *with previous T-DM1 exposure*
- Diarrhea prophylaxis with colestipol and loperamide was required during cycle 1 and provided by the sponsor.
- All pts had brain MRI + CT chest/abdomen/pelvis every 6 wks x 18 wks, then every 9 wks; ctDNA @ baseline, off tx treatment
- A patient-reported outcome (PRO) sub-study assessed GI toxicity and adherence to anti-diarrheal medication

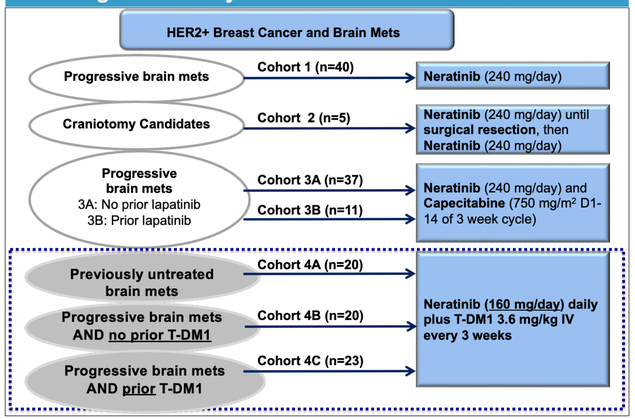
Statistical Design

- Cohorts 4A and 4B were single-stage designs with a planned enrollment of 20 patients each
- Cohort 4C had a two-stage design, with a requirement for at least 1 of the first 9 pts to achieve a response in order to enroll a total of 24 patients.
- The primary endpoint = RANO-BM (Response Assessment in Neuro-Oncology-Brain Metastases) in each cohort separately.
- Correlative studies included patient-reported outcomes (PROs) for gastrointestinal toxicity (data forthcoming).

Cohort 4 Participating Centers

Dana-Farber Cancer Institute, Massachusetts General Hospital, Johns Hopkins, U of Michigan, UCSF, Mayo, UPMC, UNC, Georgetown, Baylor

Figure 1. Study Cohorts to Date – TBCRC 022



Key Eligibility – Cohorts 4A, 4B, 4C

- Measurable parenchymal brain metastases, 10+ mm; HER2+ metastatic breast cancer (MBC) by local review
- No limit on prior CNS treatments or lines of therapy for MBC but no prior neratinib
- No pre-existing grade ≥2 active/chronic diarrhea
- Left ventricular ejection fraction >/=50%
- No escalation of steroids or uncontrolled seizures over the last 7 days, ECOG PS 0-2

During 11/07/2018-11/01/2021: 6, 17, and 21 pts enrolled to cohorts 4A, 4B, and 4C, respectively; *enrollment terminated early due to slow accrual.*

Table 1. Patient Characteristics

Characteristic	Cohort 4A (n=6)	Cohort 4B (n=17)	Cohort 4C (n=21)
Age (median, range)	52 (44-65)	48 (42-59)	48 (35-68)
Non-white race	2 (33.0)	3 (17.6)	1 (4.8)
# of prior chemo lines for MBC	Median = 2 (range 0-10)		
1	1 (16.7)	9 (52.9)	0 (0)
2	1 (16.7)	4 (23.5)	6 (28.6)
3+	1 (16.7)	3 (17.6)	15 (71.4)
Missing	3 (50)	1 (5.9)	0 (0)
Prior tucatinib	0 (0)	0 (0)	0 (0)
Prior CNS surgery	0 (0)	7 (41.2)	7 (33.3)
Prior WBRT	0 (0)	12 (70.6)	11 (52.4)
Prior SRS	1 (16.7)	12 (70.6)	10 (47.6)

Table 2. Best RANO-BM CNS Response

Response	Cohort 4A	Cohort 4B	Cohort 4C
CR	0 (0)	1 (5.9)	0 (0)
PR	2 (33.3)	4 (23.5)	6 (28.6)
Unconfirmed PR	1 (16.7)	0 (0)	2 (9.5)
SD	2 (33.3)	8 (47.1)	10 (47.6)
PD	0 (0)	0 (0)	1 (4.8)
Unavailable (off tx before imaging)	1 (16.7)	3 (17.6)	2 (9.5)
CNS ORR	**33.3% (4.3-77.7%)**	**29.4% (10.3-56.0%)**	**28.6% (11.3-52.2%)**
CNS CR + PR + SD ≥6 mos	50% (11.8-88.2%)	35.3% (14.2-61.7%)	33.3 (14.6-57.0%)

Figure 2. Waterfall Plot- % CNS Response

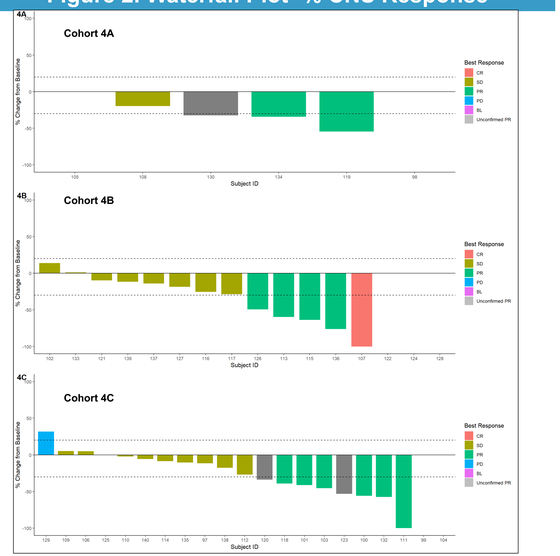


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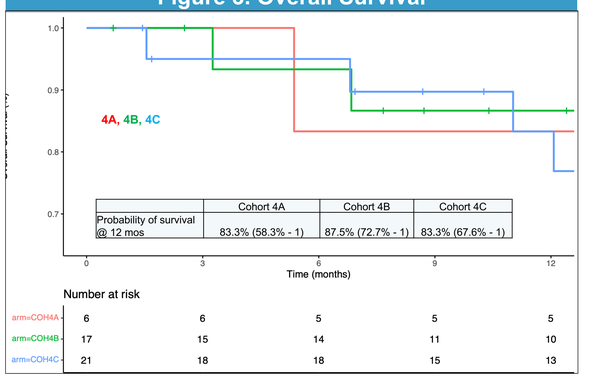
Table 3. Adverse Events Across 4A,4B,4C (n=44)

Adverse Event	Grade 2 (n,%)	Grade 3 (n, %)	Grade 4 (n, %)
Diarrhea	14 (32)	10 (23)	
Fatigue	11 (25)	1 (2)	
Aspartate aminotransferase increased	6 (14)	3 (7)	
Nausea	7 (16)	1 (2)	
Alanine aminotransferase increased	2 (5)	2 (5)	1 (2)
Anorexia	5 (11)	--	
Platelet count decreased	4 (9)	1 (2)	
Vomiting	4 (9)	--	
Abdominal pain	3 (7)	--	
Dehydration	1 (2)	2 (5)	
Dyspepsia	3 (7)	--	
Gastroesophageal reflux disease	3 (7)	--	
Hypokalemia	--	3 (7)	
Mucositis oral	3 (7)	--	
Anemia	--	2 (5)	
Generalized muscle weakness	2 (5)	--	
Peripheral sensory neuropathy	1 (2)	1 (2)	

Figure 3. Overall Survival



Probability of survival @ 12 mos	Cohort 4A	Cohort 4B	Cohort 4C
	83.3% (58.3% - 1)	87.5% (72.7% - 1)	83.3% (67.6% - 1)

Conclusions

- Intracranial activity was observed for the combination of neratinib plus T-DM1 across Cohorts 4A-4C, including those with prior T-DM1 exposure, suggesting a reversal of resistance to T-DM1.
- Even with prophylaxis, grade 2-3 diarrhea events still occurred
- Our data provide additional evidence for consideration of neratinib-based combinations in pts with HER2+ BCBM.