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Supplementary information

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Tucatinib–trastuzumab–capecitabine for treatment of leptomeningeal metastasis in women with HER2^{+} breast cancer: TBCRC049 phase 2 study results

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Supplementary Table 1. Clinical, Cytologic, Radiographic, and Composite Responses in Patients with Leptomeningeal Metastasis. Each row represents an individual response evaluable patient, and columns summarize key response categories. Of the 13 response assessment-eligible patients, 5 achieved a composite response and all achieved clinical benefit, defined as stable disease or better. Four of the 17 enrolled patients were non-evaluable for response due to one discontinuing for liver toxicity, one opting for hospice, and two with symptoms indicating progressive LMD, all prior to first restaging.

Status at Re-staging

Green denotes Improved/CR/PR | Yellow denotes Stable/SD | Pink denotes Worse/PD

	Clinical LM Response (Target Deficits)*	CSF Cytologic Response	Best Radiographic LM Response	Composite LM Response
Patient 1	Improved	Stable (negative)	SD	Stable
Patient 2	Stable	Stable (negative)	SD	Stable
Patient 3	Stable	No data	SD	Stable
Patient 4	Improved	Stable (negative)	PR (C5)	Response
Patient 6	N/A (no target deficits)	Response (positive → negative)	SD	Stable
Patient 7	Improved	No data	PR	Response
Patient 8	Improved	Response (positive → negative)	PR (C3) → CR (C9)	Response
Patient 9	Improved	Stable (negative)	PR	Response
Patient 10	Improved	Stable (negative)	SD	Stable
Patient 11	Stable	Stable (atypical → negative)	SD	Stable
Patient 13	Stable	Stable (positive)	SD	Stable
Patient 14	Stable	Stable (atypical → negative)	SD	Stable
Patient 17	Improved (C6)	Stable (atypical → negative)	PR	Response

*At first re-staging (prior to Cycle 3 unless otherwise noted)
^Four patients were non-evaluable for response: 1 discontinued early for toxicity, 1 patient choice, and 2 PD
C: cycle | CR: complete response | PR: partial response | PD: progressive disease | SD: stable disease

Supplementary Table 2. Leptomeningeal Metastasis (LM) Composite Response Assessment Criteria.

	LM Composite Response = All Three			
Assessment	Response	Progressive or Refractory Disease		Stable disease
		Neuro/clinical defined progression	Radiologic defined progression	
Neurological clinical evaluation	Improved or stable target deficits*	Worse	Stable or worse	Stable
CSF cytology	Negative^ (when positive at baseline)	Negative or positive		
CNS imaging	Radiologic PR or CR	Stable	Progressive disease	Stable

CR: complete response | PR: partial response
*Up to 4 target deficits (neurologic signs or symptoms) attributed to LM and identified at baseline (if present)
^Confirmed on subsequent CSF evaluation

Supplementary Table 3. Most Common Adverse Events by Severity.

Adverse Events (n)	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	9	4*	0	0
Fatigue	3	6*	0	0
Nausea/Vomiting	6	1	1[a#]	0
Hand-foot syndrome	5	7	1[b]	0
Liver function test elevation[c]	5[d]	2[e]	3[f]	1[g#]

*One of these events was a serious adverse event.
[#]Event led to discontinuation of study drug.
ALT: alanine aminotransferase; AST: aspartate aminotransferase
a. Study treatment held and resolved to Grade 1 in 24 hours
b. Resolved to Grade 1 with hold of capecitabine, managed with dose reduction of capecitabine
c. Refers to AST/ALT elevation unless otherwise noted
d. 2 patients with Grade 1 total bilirubin elevation in addition to Grade 1 AST and ALT elevations 3 patients with Grade 1 Alkaline phosphatase in addition to Grade 1 AST and ALT elevations
e. 1 patient with Grade 2 total bilirubin elevation in addition to Grade 2 AST
f. 1 patient with Grade 3 AST and ALT elevation (concurrent Grade 1 total bilirubin elevation) - study treatment discontinued due to CNS progression – LFTs normalized within 1 month of study discontinuation; 1 patient with Grade 3 ALT elevation (concurrent Grade 2 AST elevation): resolved to grade 1 with treatment hold - resumed treatment with dose reduction; 1 patient with Grade 3 ALT elevation (concurrent Grade 2 AST elevation and Grade 1 total bilirubin elevation).
g. 1 patient with ALT elevation after 1 cycle that led to treatment discontinuation and resolved after 1 month