

Managing Brain Metastases in HER2+ MBC:

A Look at the Latest Evidence on HER2-Targeted Therapy

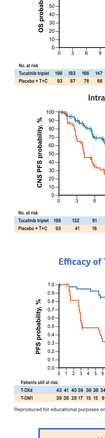
KEY CLINICAL TRIALS IN HER2+ BREAST CANCER WITH BMs

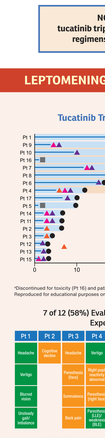
Therapy	Key Clinical Trial(s)	Study Population	CNS Outcomes	Safety
Tucatinib + Trastuzumab + Capecitabine ("Tucatinib Triplet")	HER2CLIMB[1,2]	N=612; randomized 2:1 to tucatinib triplet vs placebo + T+C; 48% vs 46% had baseline BM (active/stable; untreated/progressing)	• IC-PFS (BM cohort): 9.9 vs 4.2 mo • 45% ↓ risk of new brain lesions • ORR-IC ~47% • mOS 21.4 vs 11.8 mo (active BMs)	Diarrhea, PPE, nausea, anemia; GI toxicity from capecitabine + tucatinib
T-DXd	DESTINY-Breast03 (randomized)[3,4] DESTINY-Breast12 (single-arm BM cohort)[5]	N=524; prior 1st-line trastuzumab + taxane; BM subgroup n=82 (stable/active); randomized to T-DXd vs T-DM1 N=504; 263 with BM (stable/active); ≥2 prior metastatic lines; tucatinib-naive	• mPFS (BM cohort): 15.0 vs 3.0 mo • 12-mo PFS 72.0% vs 20.9% (HR 0.25) • 12-mo CNS PFS 58.9% • CNS ORR 71.7% (stable 67%, active 60.7%)	ILD/pneumonitis (~10%-16%, mostly grade 1-2; rare fatal), nausea, cytopenias ILD/pneumonitis (~10%-16%, mostly grade 1-2; rare fatal), nausea, cytopenias
Neratinib + Capecitabine	NALA[6]	HER2+ MBC; ≥2 prior HER2-directed regimens; ~16% with baseline CNS metastasis (treated/untreated); allowed stable/asymptomatic CNS disease; randomized to N+C vs L+C	• CNS intervention: 22.8% vs 29.2% (p = .043) • Delayed CNS progression/intervention vs control; no ORR-IC reported	Higher incidence of diarrhea with N+C (grade ≥3: 24.4%) vs L+C; manageable with prophylaxis
Lapatinib + Capecitabine	LANTERN[7]	HER2+ MBC; newly diagnosed/recently progressed CNS metastasis post-local therapy; prior trastuzumab; randomized to L+C vs T+C (n=30)	• Median CNS PFS: 26.7 wk vs NE • CNS ORR: 25% vs 71%	High rates of diarrhea, fatigue, PPE; more SAEs with L+C (56%) vs T+C (21%)

Multiple HER2-targeted regimens show CNS activity in HER2+ MBC, with the strongest evidence for tucatinib triplet and T-DXd. Neratinib and lapatinib also remain options in select cases.

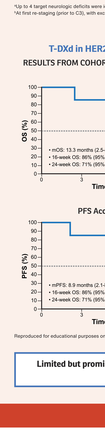
TUCATINIB TRIPLET AND T-DXd DEMONSTRATE DURABLE INTRACRANIAL CONTROL IN STABLE AND ACTIVE BM

HER2CLIMB: Efficacy of Tucatinib Triplet Therapy in Patients With BM[2]





DESTINY-BREAST03: Efficacy of T-DXd + Taxane in Patients With BM[4]

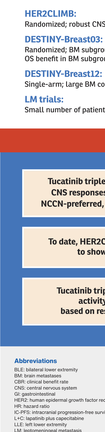


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NCCN Guidelines (v4.2025) list tucatinib triplet (Category 1) and T-DXd as preferred regimens for HER2+ breast cancer with BM.[8]

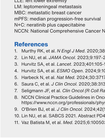
LEPTOMENINGEAL METASTASES (LM) ACTIVITY

Phase 2 TBCRC049: Tucatinib Triplet for HER2+ Breast Cancer LM[9,10]



*Discontinued for toxicity (Pt 16) and patient choice (Pt 5).
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7 of 12 (58%) Evaluable Patients With Target Deficits at Baseline Experienced Improvement of Deficits*



*Up to 4 target neurologic deficits were identified for each patient.
†At first re-staging (prior to C3), with exception of Pt 17 (prior to C6).

DEBBRAH Cohort 5: T-DXd in HER2+ or HER2-Low Breast Cancer and LM[11]

RESULTS FROM COHORT 5: HER2-positive or HER2-low MBC with LM (n=7)

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Limited but promising data support tucatinib triplet and T-DXd in patients with LMs.

STUDY CAVEATS

HER2CLIMB:
Randomized; robust CNS data; included untreated and progressing BM

DESTINY-Breast03:
Randomized; BM subgroup analysis not powered for CNS endpoints; OS benefit in BM subgroup not statistically significant

DESTINY-Breast12:
Single-arm; large BM cohort; no head-to-head with other CNS-active regimens

LM trials:
Small number of patients; exploratory

KEY TAKEAWAYS

Tucatinib triplet and T-DXd provide clinically meaningful CNS responses in HER2+ breast cancer with BM and are NCCN-preferred, with tucatinib triplet designated Category 1

To date, HER2CLIMB is the only randomized phase 3 trial to show an OS benefit in patients with BM

Tucatinib triplet and T-DXd have shown encouraging activity in LM from HER2+ breast cancer, based on results from small but promising studies

Abbreviations

BLE: bilateral lower extremity
BM: brain metastases
CBR: clinical benefit rate
CNS: central nervous system
GI: gastrointestinal
HER2: human epidermal growth factor receptor 2
HR: hazard ratio
IC-PFS: intracranial progression-free survival
L+C: lapatinib plus capecitabine
LLE: left lower extremity
LM: leptomeningeal metastasis
MBC: metastatic breast cancer
mPFS: median progression-free survival
N+C: neratinib plus capecitabine
NCCN: National Comprehensive Cancer Network
NE: not estimated
NR: not reported
ORR: objective response rate
ORR-IC: intracranial objective response rate
OS: overall survival
PFS: progression-free survival
PPE: palmar-plantar erythrodysesthesia
RANO-BM: Response Assessment in Neuro-Oncology for Brain Metastases
RECIST: Response Evaluation Criteria in Solid Tumors
SAE: serious adverse event
T+C: trastuzumab + capecitabine
T-DM1: trastuzumab emtansine
T-DXd: trastuzumab deruxtecan

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