

1767R0

BRIDGET: A phase II trial of tucatinib added to trastuzumab/pertuzumab or ado-trastuzumab emtansine after isolated intracranial progression in patients with advanced HER2-positive breast cancer

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Background

Isolated CNS relapse/progression (ICP) is a frequent occurrence in patients (pts) with HER2+ MBC. Current guidelines recommend local therapy and continuation of same systemic regimen. The impact of adjusting the systemic regimen to include a CNS-active agent is unknown. Tucatinib demonstrated significant intracranial activity in HER2CLIMB when delivered with capecitabine/trastuzumab. BRIDGET is a prospective trial to add a brain-penetrant TKI post radiation to ongoing therapy in attempts to prolong intracranial disease control in pts with stable or no extracranial disease (ECD).

Methods

Single-arm phase II trial of pts with HER2+ MBC experiencing a first or second isolated intracranial event with stable/no ECD on HP or T-DM1 within 12 wks of stereotactic radiosurgery (SRS). Key eligibility: ECOG PS 0–2; SRS to all brain lesions ≥ 5 mm, no prior HER2/EGFR TKI. Whole-brain radiation was exclusionary. Tucatinib 300 mg BID was added continuously to ongoing HP or T-DM1 therapy. Primary endpoint: intracranial PFS (iPFS) per RANO-BM compared with a historical exponential control (median of 5.0 mos) using a one-sample log-rank test (one-sided $\alpha=0.05$; 90% power; N=43 evaluable).

Results

Of 48 enrolled pts, 47 were evaluable (median age 53.5 yrs; 66% ER+). Most pts (66%) had no ECD at enrollment, were treated with backbone HP (93.6%) and enrolled after their first intracranial event (80.9%). At a median follow-up of 19.6 mos (95% CI 15.6–26.1), intracranial progression occurred in 17 pts (36.2%); median iPFS was not reached (one-sample log-rank $p<0.0001$ for H_0 : median iPFS=5 mos). The 6-, 12-, and 18-mo iPFS rates were 91%, 64%, and 59%, respectively. Extracranial progression was rare (2 pts, 4.3%). The safety profile was favorable: grade ≥ 3 adverse events occurred in 15% (7/47).

Conclusions

The addition of tucatinib to HP after radiation met the study's primary endpoint, with more than half of patients remaining free of intracranial progression at 18 months. These findings support the addition of early tucatinib after local therapy as a well-tolerated strategy to improve intracranial disease control in a HER2+ isolated brain progression population.

Clinical trial identification

NCT05323955.

Legal entity responsible for the study

Carey Anders MD.

Funding

Investigator Sponsored Trial with Pfizer Funding.

Disclosure

S. Sammons: Financial Interests, Personal, Advisory Board: Astra Zeneca, Novartis, Foundation Medicine, Daichii Sankyo, Sermonix, Pfizer, Inc., Gilead; Financial Interests, Institutional, Coordinating PI: Astra Zeneca, Eli Lilly; Financial Interests, Institutional, Local PI: Sermonix, Iambic; Financial Interests, Coordinating PI: seagen; Financial Interests, Institutional, Funding: Stemline. N.U. Lin: Financial Interests, Personal, Advisory Board, Ad board participation: Seattle Genetics, Daiichi-Sankyo; Financial Interests, Personal, Advisory Board, Ad board/Steering Committee participation; consultant: Astrazeneca; Financial Interests, Personal, Advisory Board, Ad board/Steering committee participation; travel support: Olema Pharmaceuticals; Financial Interests, Personal, Other, High level Consulting: Artera Inc.; Financial Interests, Personal, Other, Steering committee: Stemline/Menarini; Financial Interests, Personal, Advisory Board, Advisory board participation: Eisai; Financial Interests, Personal, Other, Consulting: Shorla Oncology; Financial Interests, Personal, Royalties, Royalties for book chapter(s): Up to Date; Financial Interests, Institutional, Funding, Trial funding to institute (and steering committee): Olema Pharmaceuticals, Astrazeneca, Seattle Genetics; Financial Interests, Institutional, Funding, Trial funding to institute: Zion Pharmaceuticals; Financial Interests, Institutional, Funding, trial funding to institute: Pfizer, Genentech; Financial Interests, Institutional, Funding, Trial funding for study to institute: Merck; Other, Other, Travel Reimbursement: Olema Pharmaceuticals, AstraZeneca, Daiichii Sankyo. C. Anders: Financial Interests, Personal, Invited Speaker: Genentech, Eisai; Financial Interests, Personal, Advisory Board: Seattle Genetics, AstraZeneca, Novartis, Immunomedics, Roche; Financial Interests, Personal, Royalties: UpToDate, Jones and Bartlett; Financial Interests, Institutional, Local PI, UNC CH: PUMA Biotechnology; Financial Interests, Institutional, Local PI, JPBO study: Lilly; Financial Interests, Institutional, Coordinating PI, LCCC 1525: Merck; Financial Interests, Institutional, Local PI, Her2Climb: Seattle Genetics; Financial Interests, Institutional, Local PI: Nektar Therapeutics, Tesaro, G1 Therapeutics; Financial Interests, Institutional, Local PI, Phase 1 study of ZN-1041: Zion; Financial Interests, Institutional, Coordinating PI, Ascendant study: Novartis; Financial Interests, Institutional, Local PI, BRAF inhibitor, Phase 1 and BRIDGET study: Pfizer; Financial Interests, Institutional, Local PI, Destiny Breast Studies: AstraZeneca; Financial Interests, Institutional, Local PI, Phase 1: Elucida Oncology; Financial Interests, Institutional, Research Grant, Brain Mets Predictor: Carisma Therapeutics; Financial Interests, Institutional, Local PI, Phase 1 CDK2 inhibitor: Incyclix; Financial Interests, Institutional, Local PI, Now BeOne; Phase 1 CDK4 inhibitor: BeiGene. All other authors have declared no conflicts of interest.

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