



The HER2 Flip: HER2 amplification of Tumor Cells in the Cerebrospinal Fluid (CSF-TCs) of Patients with Leptomeningeal Metastasis having solid tumors; implications for treating the LM tumor with anti-HER2 therapy



ROBERT H. LURIE
COMPREHENSIVE CANCER CENTER
OF NORTHWESTERN UNIVERSITY

Priya Kumthekar¹, MD., Michael Youssef², MD., Akanksha Sharma³, MD., Nicholas Blondin⁴, MD., Amir Azadi⁵, MD., David Piccioni⁶, MD., Michael Glantz⁷, MD., Jose Carillo⁸, MD., Nicholas Avgeropoulos⁹, MD., Sherif Makar¹⁰, MD., Barbara Blouw¹¹, PhD, Anna Natasha¹¹, Deanna Fisher¹¹, MSC, Lan Huynh¹¹, John Peters¹¹, Mariko Matsutani¹¹, Nathan Sweed¹¹, MD., Michael Dugan¹¹, MD, and Santosh Kesari⁸, MD., PhD.

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Background

- Leptomeningeal Metastasis (LM) is a devastating complication of cancer with limited treatment options.
- Assessment of the CSF to identify actionable mutations is currently not Standard Of Care
- LM Breast Cancer patients with HER2 positive primary tumors treated with IT Trastuzumab experience clinical benefit (Malani, 2020) and improved overall survival of 10.5 months with limited toxicity (Kumthekar, 2022).
- CNSide™ is a platform intended to determine the presence, quantity and biomarker characterization of malignant cells in the CSF.
- Here we present results of a retrospective analysis of HER2 amplification in the CSF of patients with LM having breast cancer, Non-Small Cell Lung Cancer (NSCLC) as well as upper GI Cancer.

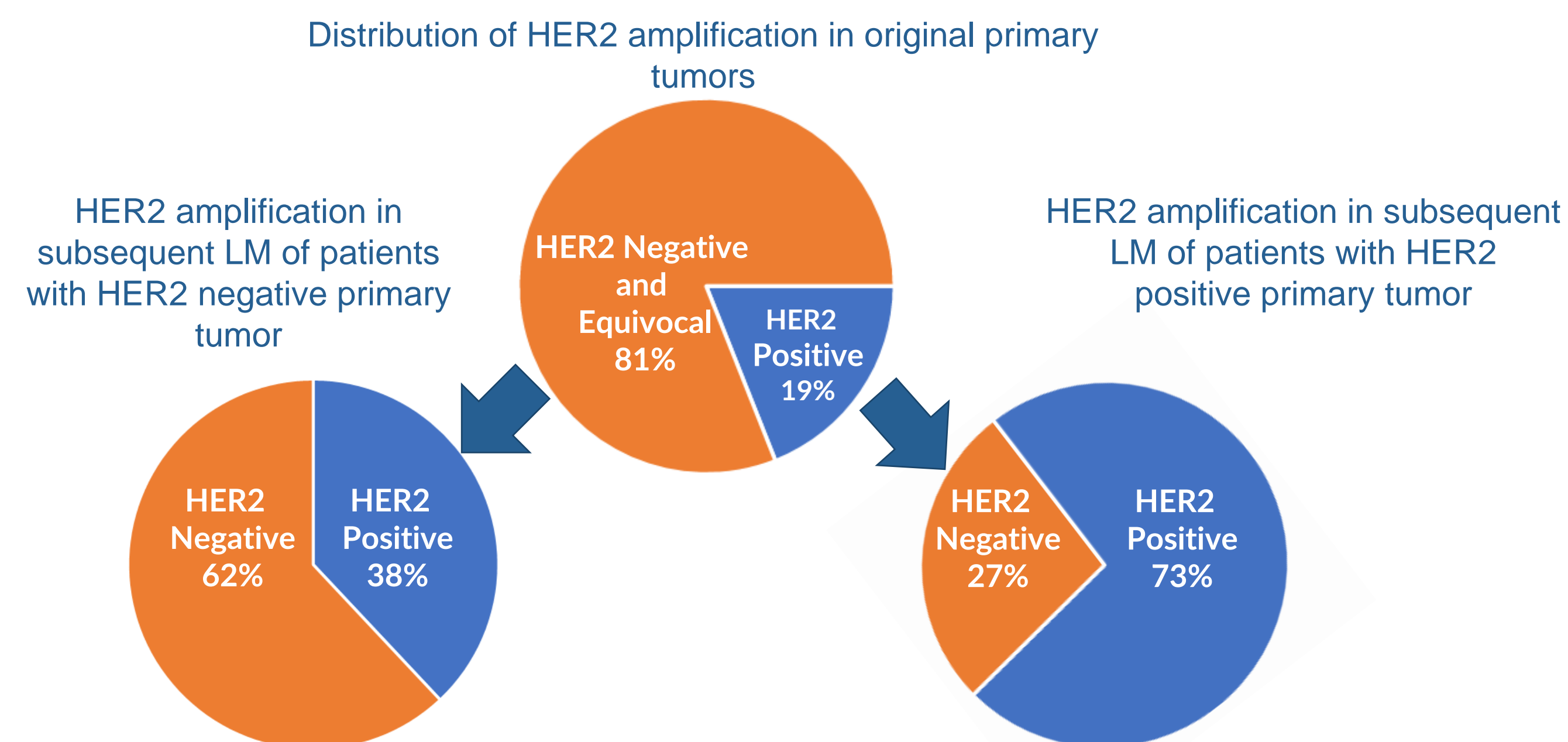
Methods

- CSF was collected from patients with suspected or confirmed LM having breast cancer (N=134 patients), NSCLC (N=28 patients), or upper GI cancer (N = 2 patients)
- CSF tumor cells were captured using a 10-antibody capture cocktail and immobilized in a streptavidin coated microfluidic channel. Cancer cells were identified with various Immunocytochemistry markers (e.g. Cytokeratin, CD45) and hybridized with a probe detecting HER2 or CEP17.
- Cells were deemed HER2 amplified if the ratio of HER2 to CEP17 ≥ 2 , or if ≥ 6 copies of HER2 were detected.
- For each sample between 50 randomly chosen, or all cells were evaluated for HER2 amplification

Patient Characteristics

Characteristics	N
Breast Cancer	134
HER2 Positive Primary Tumor	26
HER2 Negative Primary Tumor	95
HER2 Equivocal (2+) Primary Tumor	13
TN	31
ER+/PR+	56
ER+/PR+/HER2+	11
Patients for which ER/PR/HER2 status is unknown	36
NSCLC	28
Adenocarcinoma	21
Adenosquamous Cell Carcinoma	1
Unkown	6
Upper GI	2
GE Junction Carcinoma	1
Esophageal Cancer	1

HER2 Flip in LM of Breast Cancer Patients



- Primary tumors were assessed for HER2 status per Immunohistochemistry and LM tumors of matched patients were analyzed for HER2 amplification in CSF TCs by FISH
 - 81% (108/134) of the patients had a HER2 negative or equivocal primary tumor
 - 19% (26/134) had a HER2 positive primary tumor
 - 38% (41/108) patients with a HER2 negative or equivocal primary tumor switched to a HER2 positive LM
 - Six (6) of these patients were treated with anti-HER2 targeted therapy
 - 27% (7/26) of the patients with a HER2 positive primary tumor switched to a HER2 negative LM
- Analysis based on concordance/discordance between the primary tumor and LM (combining HER2 equivocal primary tumors with HER2 negative primary tumors):
 - 64% (86/134) of the patients had concordant HER2 status between the primary tumor and LM
 - 36% (48/134) had discordant HER2 status between the primary tumor and LM
 - Of the patients having HER2 discordant primary tumor and LM status:
 - 85% (41/48) had a HER2 negative primary tumor and HER2 positive LM
 - 15% (7/48) had a HER2 positive primary tumor and a HER2 negative LM

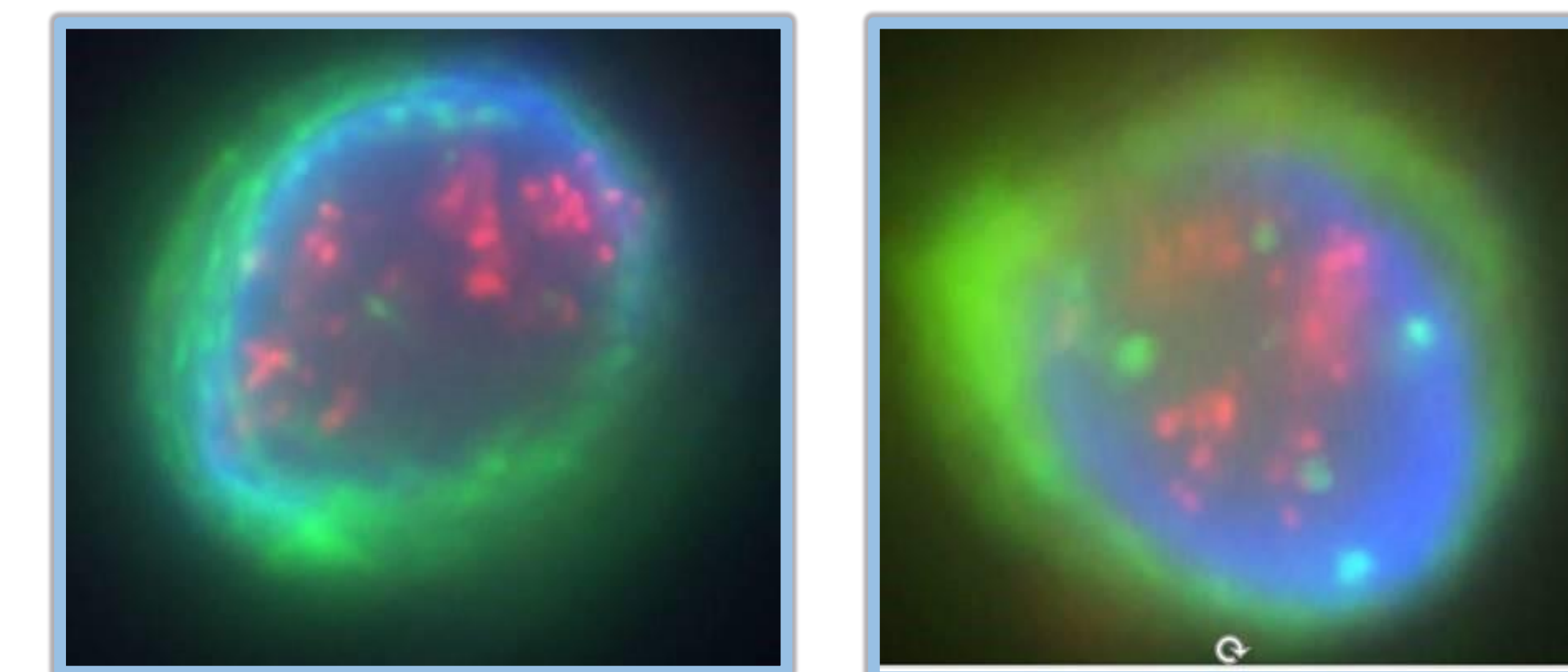
HER2 Amplification in the LM of NSCLC and Upper GI Patients

Tumor Type	Primary Tumor HER2 Status	Subsequent LM HER2 Status
NSCLC (N=28)	Not Tested	50% Positive (14/28)
GE Junction Carcinoma (N=1)	Positive	Positive
Esophageal Cancer (N=1)	Equivocal (2+)	Positive

Detection Range of HER2 amplified CSF Tumor Cells

Tumor Type	Range of number HER2 positive CSF TCs
Breast Cancer	1-80 (Average is 7 HER2 + cells/patient)
NSCLC	1-32 (Average is 12 HER2 + cells/patient)
GE Junction Carcinoma	53
Esophageal Cancer	50

Examples of HER2 Amplification by FISH in CSF



Conclusions

- HER2 amplification in the CSF is detected in a substantial fraction of CSF-TCs from patients with LM having breast, upper GI and NSCLC cancer and potential other solid tumors
- An increased HER2 positivity in LM may imply HER2 is a driver for developing LM
- Prospective studies are needed to determine if evaluation of HER2 amplification in the CSF of patients with LM having solid tumors should be routinely considered, as this may offer viable treatment options otherwise not considered

References

Malani R, Fleisher M, Kumthekar P, Lin X, Omuro A, Groves MD, Lin NU, Melisko M, Lassman AB, Jayapalan S, Seidman A, Skakodub A, Boire A, DeAngelis LM, Rosenblum M, Raizer J, Pentsova E. Cerebrospinal fluid circulating tumor cells as a quantifiable measurement of leptomeningeal metastases in patients with HER2 positive cancer. *J Neurooncol.* 2020 Jul;148(3):599-606. doi: 10.1007/s11060-020-03555-2. Epub 2020 Jun 6. PMID: 32593669; PMCID: PMC7438284.

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