Anti-HER3 antibody, HMBD-001, in combination with an EGFR inhibitor effectively inhibits tumor growth in biomarker selected pre-clinical models of squamous cell carcinomas

#2659

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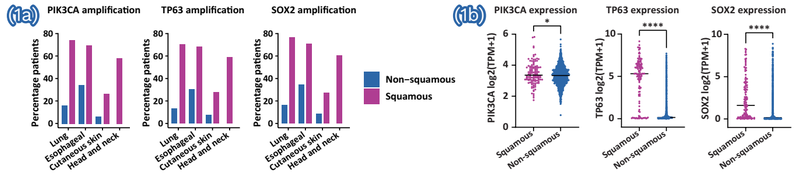
Background and rationale

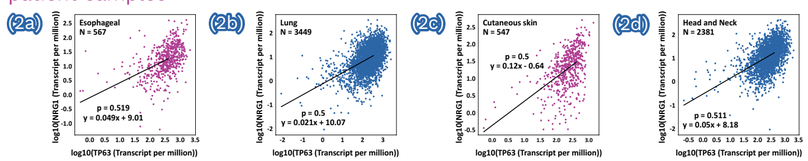
- Squamous cell carcinomas (SCCs) arise from epithelial tissues and share a common etiology
- Environmental insults generate common genetic aberrations, such as amplification of Chr 3q and loss of Chr 3p, which are hallmarks of early oncogenesis in SCCs[1]
- Chr 3q amplification leads to increased transcriptional activity of
  - TP63, which directly promotes HER3 ligand (NRG1) expression[2]
  - SOX2, which directly promotes expression of EGFR ligands[3]
  - PIK3CA, enhancing activation of the PI3K pathway
- Chr 3p loss leads to deletion of several putative tumour suppressor proteins, including TUSC2, an inhibitor of EGFR[4]
- Chr 7p encoding EGFR has also been found to be frequently amplified in squamous cell carcinomas[5,6,7]
- Inhibition of EGFR has been shown to lead to compensatory increases in HER3/pHER3 leading to increased PI3K pathway activity and resistance to EGFR monotherapy[8]
- Inhibition of HER3 signaling, alone or in combination with EGFR inhibitions, may therefore have broad applicability in SCCs
- HMBD-001, a differentiated and potentially best-in-class HER3-targeting antibody that blocks HER3 heterodimers with EGFR to potently inhibit PI3K signaling, is currently being investigated in Phase 1 trials (NCT05057013)

Chr 3q genes involved in HER signaling are frequently amplified and have higher expression in squamous compared to non-squamous cancers



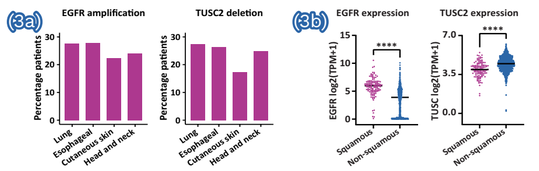
(1a) Percentage of squamous and non-squamous patient samples with PIK3CA, TP63 and SOX2 copy number amplification (Copy number > 3), obtained from Caris's squamous lung, esophageal, cutaneous skin and head and neck cancer datasets. (1b) Expression levels of PIK3CA, TP63 and SOX2 of squamous and non-squamous cell lines, obtained from DepMap.

TP63 and NRG1 expression are positively correlated in squamous cancer patient samples



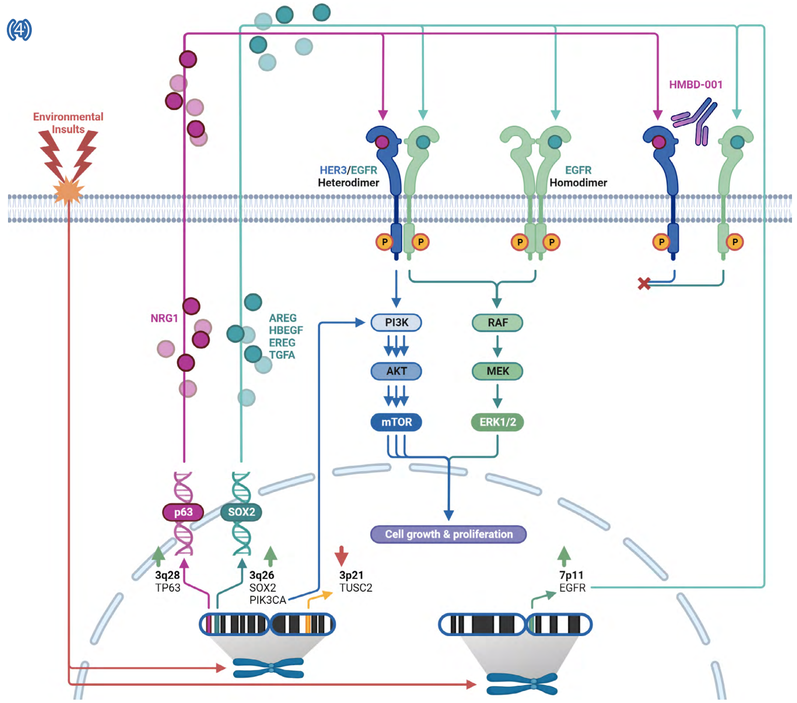
Correlation of TP63 and NRG1 in squamous (2a) esophageal, (2b) lung, (2c) cutaneous skin, and (2d) head and neck cancer patient samples, obtained from Caris data set.

EGFR on chr 7p is frequently amplified and upregulated, while the negative regulator of EGFR signaling, TUSC2 on chr 3p is deleted and downregulated in squamous cancers

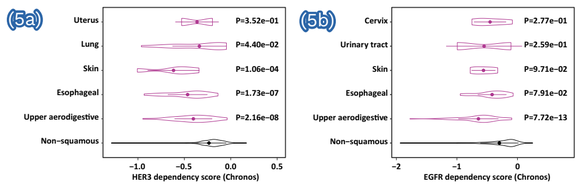


(3a) Percentage of squamous patient samples with EGFR amplification (copy number > 3) and TUSC2 loss (copy number < 0.5), obtained from Caris's squamous lung, esophageal, cutaneous skin and head and neck datasets. (3b) Expression levels of EGFR and TUSC2 of squamous and non-squamous cell lines, obtained from DepMap.

A unifying hypothesis of etiology and tumorigenesis in squamous cell carcinoma and role of anti-HER3 therapeutics

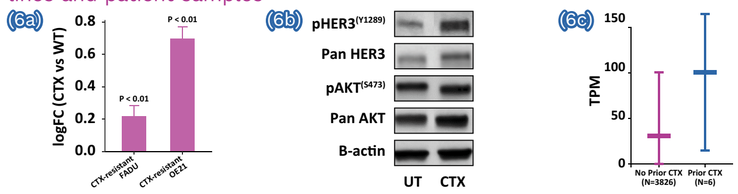


Squamous cancer cell lines are strongly dependent on HER3 and weakly dependent on EGFR



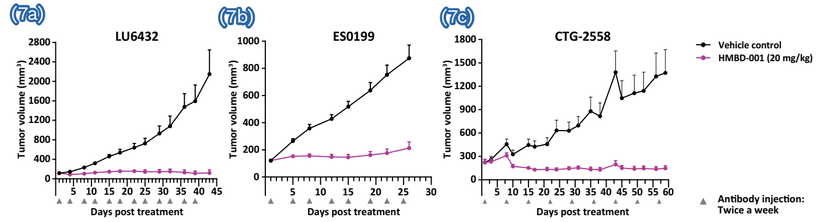
Comparison of (5a) HER3 and (5b) EGFR dependency score (Chronos) of squamous to non-squamous cancer cell lines, obtained from DepMap.

Inhibition of EGFR results in compensatory increases in HER3 signaling in cell lines and patient samples



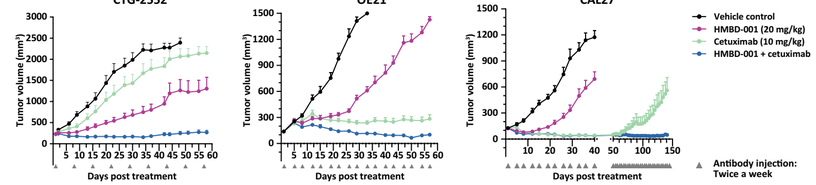
(6a) HER3 mRNA level in cetuximab-resistant squamous cell lines as compared to parental cell lines (FADU and OE21). (6b) HER3/AKT signaling protein levels in post-cetuximab treated squamous NSCLC HARA cell line. (6c) HER3 mRNA level in squamous lung cancer patients with and without prior cetuximab treatment, obtained from Caris's data set; WT: wild-type, CTX: cetuximab, UT: untreated.

Squamous models with TP63 amplification show robust monotherapy response to HMBD-001



In vivo efficacy studies of (7a) sqNSCLC (LU6432), (7b) ESCC (ES0199), and (7c) sqNSCLC (CTG-2558) models with TP63 amplification treated with HMBD-001 monotherapy.

Combining HMBD-001 with cetuximab results in potent and sustained anti-tumor activity in TP63-positive and EGFR-amplified squamous models



In vivo efficacy studies of (8a) sqNSCLC (CTG-2552), (8b) ESCC (OE21), and (8c) HNSCC (CAL27) TP63-positive and EGFR-amplified squamous models treated with HMBD-001, cetuximab and HMBD-001 + cetuximab combination.

Conclusion

- Common genetic alterations that increase HER3/NRG1 and EGFR signaling are frequently observed in squamous cell carcinomas
- SCCs are more dependent on HER3 than EGFR, therefore inhibition of HER3, alone or in combination with EGFR inhibition, could have broad applicability in squamous cell carcinomas
- Inhibition of HER3 signaling with a potentially best-in-class anti-HER3 antibody HMBD-001 results in potent monotherapy anti-tumor activity across various squamous cancers
- HMBD-001 combination with EGFR inhibition could further improve efficacy in EGFR amplified SCCs
- Hummingbird Bioscience will initiate Phase 1b studies in biomarker-selected populations of SCCs in the second half of 2023

References

[1]*Hoadley KA et al, Cell (2014) 158 (4): 929-944.*

[2]*Hegde GV et al, Elife (2019) 8:e46551.*

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[8]*Wheeler DL et al, Oncogene. (2008) 27 (28):3944-3956.*

For more information on the HMBD-001 program

hummingbirdbioscience.com/hmbd-001/