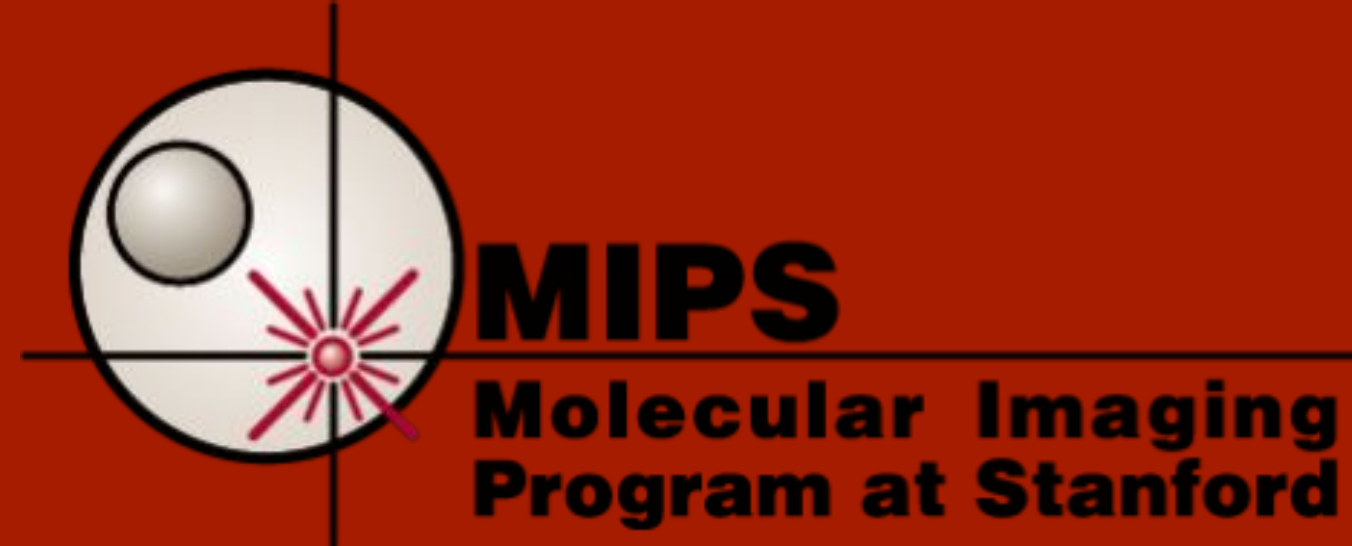




Potential of T-DM1 (Kadcyla) for treatment of Head and Neck Squamous Cell Carcinoma

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INTRODUCTION

Antibody-drug conjugates are a new and highly novel therapy that has had 5 new agents approved in the past several years. HER2 expression is low in HNSCC but present in 20% of patients. HER2-directed antibody drug conjugates are highly effective at killing tumor cells with low HER2 expressing tumors in breast cancer models. Here, we investigate the *ex vivo* and *in vivo* expression and targetability of HER2 in HNSCC with trastuzumab-emtansine (T-DM1), a commercially available anti-HER2 antibody-drug conjugate linked to a cytotoxic agent approved for metastatic breast cancer.

METHODS

Immunohistochemistry was performed on 17 human HNSCC biopsy samples to characterize HER2 expression in HNSCC patients. Tissue collection and protocol was approved by Stanford’s IRB. Western blotting was performed to assess HER2 expression in six HNSCC cell lines, compared against a HER2-breast cancer cell line (MDAMB231) and a HER2+ breast cancer cell line (BT474). Pharmacologic inhibition of HNSCC cell lines by T-DM1 was characterized by metabolic activity, as measured by MTS assay.

RESULTS

Tumor site	N =	0 IHC	2+ IHC
Oral cavity	11	11/11 (100%)	0/11 (0%)
Oropharynx	5	4/5 (80%)	1/5 (20%)*
Larynx	1	1/1 (100%)	0/11 (0%)
Total	17		

Table 1: Patient characteristics of HNSCC biopsies for HER2 expression.

RESULTS

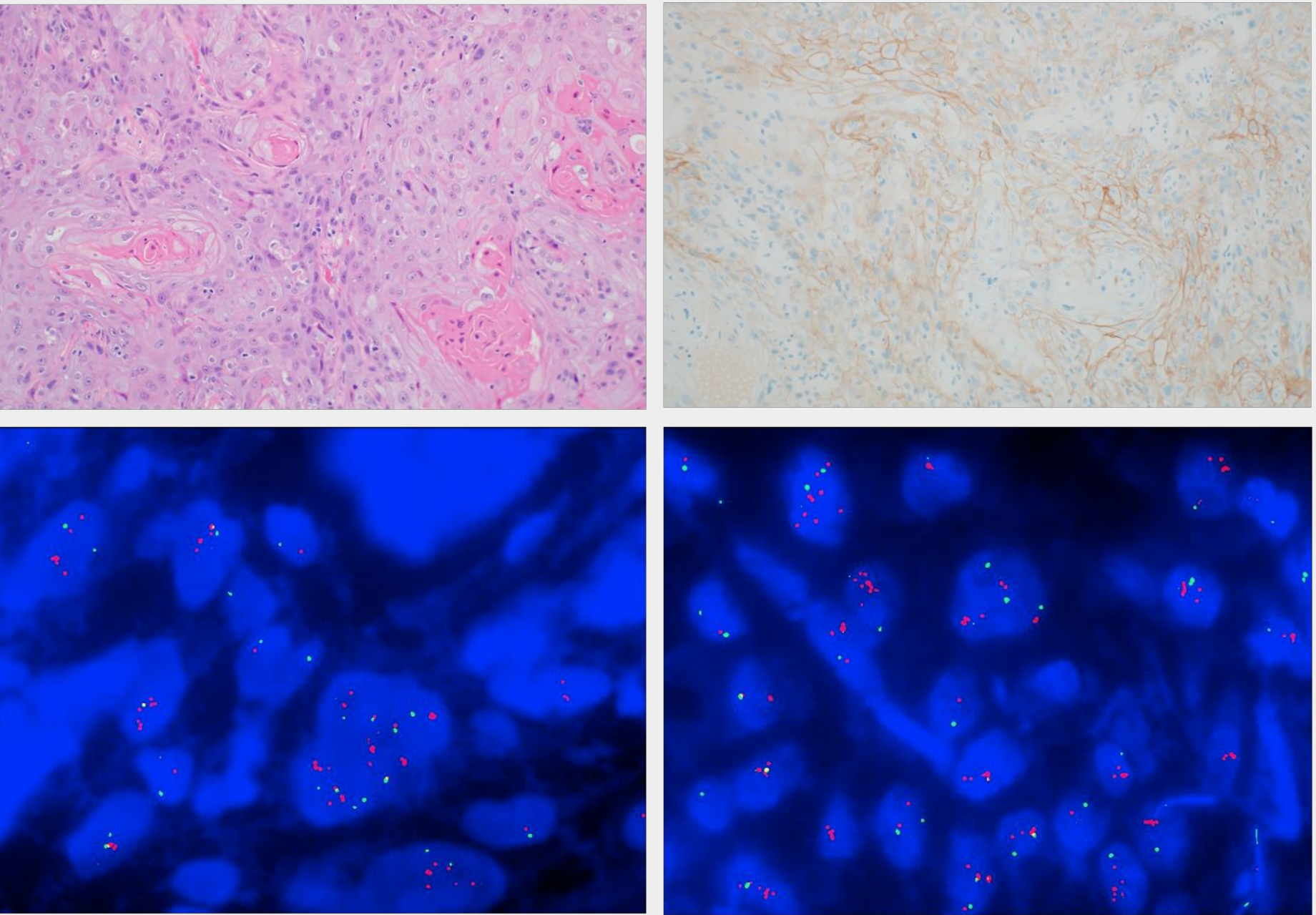


Figure 1: One out of 17 HNSCC biopsies scored 2+ for HER2 expression by IHC and confirmed by FISH. (Top, left: H&E; Top, right: IHC HER2, 2+, 60% expression; Bottom: HER2 FISH, HER2/D17Z1 ratio>2, HER2 signals/cell>4, HER2+).

Figure 2: Western blotting revealed low by consistent levels of HER2 expression relative to HER2-overexpressing breast cancer positive control.

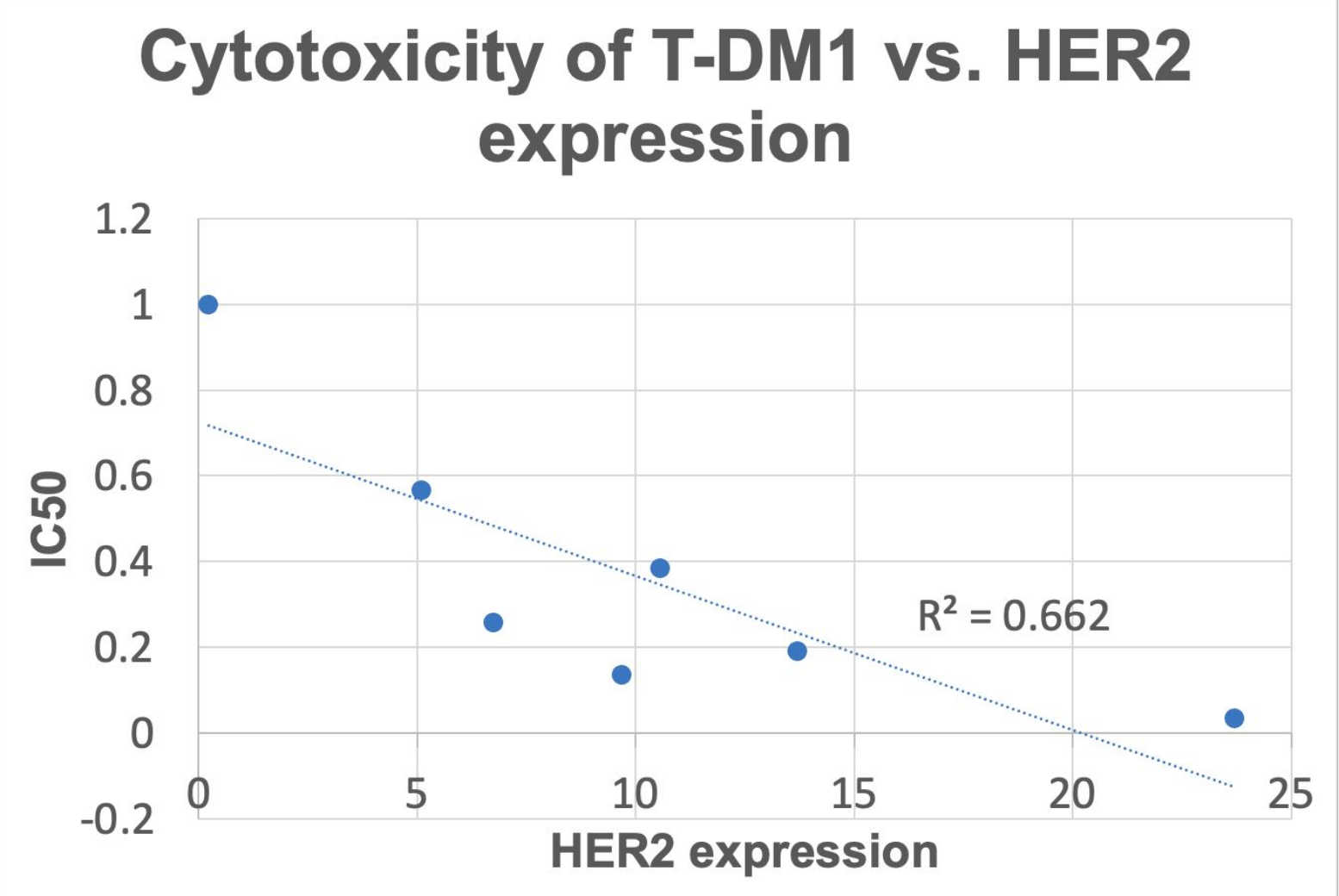
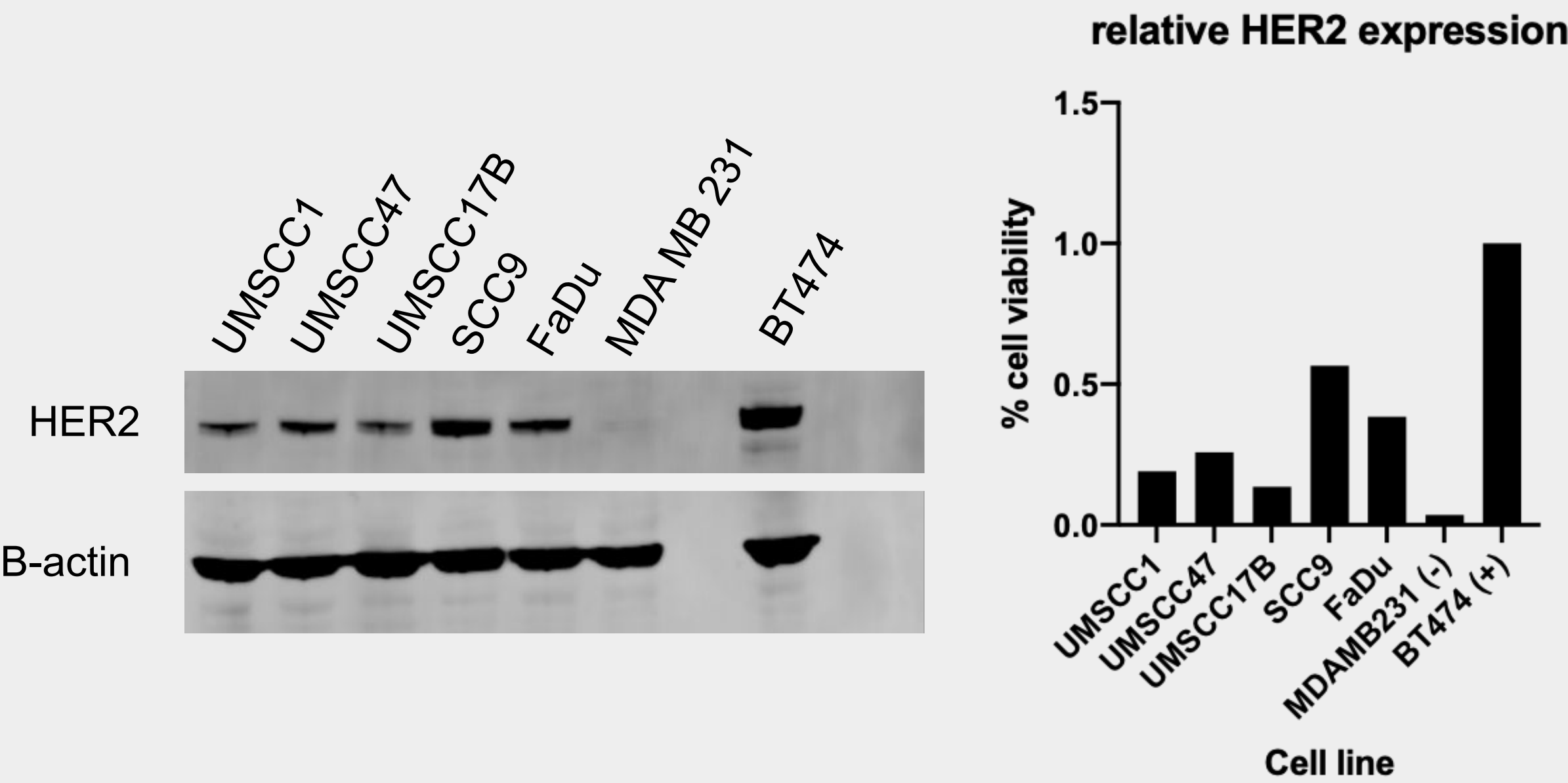


Figure 3: Cytotoxicity of TDM1 correlated with HER2 expression in HNSCC cell lines.

DISCUSSION

Eleven human HNSCC biopsy samples were from the oral cavity, five from the oropharynx, and one from the larynx. One out of the 17 (5.9%) HNSCC biopsies scored 2+ for HER2 expression by immunohistochemistry and confirmed by FISH in the oropharyngeal cohort. In cell lines, western blotting revealed low but consistent levels of HER2 expression (3.5%-56.6%) relative to a HER2-overexpressing breast cancer cell line. TDM1 sensitivity in HNSCC cell lines positively correlated with HER2 expression. HNSCC cell lines showed 2.5-fold to 4.6-fold sensitivity to TDM1 compared to HER2 negative cells. Consistent with the HER2 selectivity of T-DM1 , we found SCC9 to have the highest HER2 expression which corresponded with the lowest T-DM1 IC50. SCC25 had the lowest HER2 expression but was still mildly responsive to T-DM1 treatment, with a 2.5-fold lower IC50 compared to the HER2-negative breast cancer control.

CONCLUSION

Although HER2 is moderately expressed in HNSCC tumor samples, *In vitro* studies demonstrated that low levels of expression were sufficient for cell killing with TDM1 for HNSCC patients expressing HER2.

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