Topiramate decreases radiation cytotoxic edema in Her2+ brain metastases

**Introduction**

- 20-40% of HER2+ breast cancer patients will develop brain metastases (BrM)1.
- HER2+ patients are treated with Trastuzumab or T-DM12.
- Most patients with BM are also treated with radiotherapy (RTx), including SRS.
- Clinical evidence suggests that a combination of T-DM1 and RTx results in high rates of radionecrosis (CSRN)3.

<table>
<thead>
<tr>
<th>Brain metastases/breast cancer patients</th>
<th>SRS treatment m=45</th>
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</thead>
<tbody>
<tr>
<td>Receipt T-DM1</td>
<td>All patients</td>
</tr>
<tr>
<td>CSRN (%)</td>
<td>No CSRN (%)</td>
</tr>
<tr>
<td>No</td>
<td>22 (45.5%)</td>
</tr>
<tr>
<td>Yes</td>
<td>23 (9.1%)</td>
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To identify potential targets for intervention or mitigation of this side effect:

**Goal:** To define the mechanisms underlying brain edema and CSRN induced by RTx alone or in combination with T-DM1

- Brain edema results from cytotoxic (cellular swelling) and vasogenic (Blood-Brain Barrier (BBB) disruption) edema.
- RTx is best known to induce vasogenic edema through upregulation of VEGF leading to endothelial cell disruption.
- Cytotoxic edema is the reversible first step in the sequence of events leading to vasogenic edema and necrosis.
- Astrocytes are gatekeepers of water flow in the brain through modulation of the water channel aquaporin 4 (AQP4).

**Hypothesis:** T-DM1/RTx induces cytotoxic edema through upregulation of AQP4 in astrocytes

**Prediction:** Blockage of AQP4 would prevent astrocytic swelling – cytotoxic edema in Her2 Brain mets

**Results**

- RTx could induce endfeet astrocytic swelling as a pre cytotoxic event

**Conclusions**

- RTx induces cytotoxic edema in astrocytes.
- T-DM1 enhances RTx-induced cytotoxic edema through unintended targeting of Her2+ reactive astrocytes.
- AQP4 upregulation is associated with RTx-induced astrocytic swelling.
- Topiramate ameliorates Radiation/TDM1-increased cell swelling of astrocytes in vitro and water content in vivo.