Aim: ErbB2 is overexpressed in about 25% of breast cancers. It modulates myocardial development and function in the heart. Trastuzumab (T), an anti-ErbB2 inhibitor, has improved the prognosis of patients with breast cancer, but is related to an increased risk of asymptomatic left ventricular (LV) dysfunction (3–34%) and heart failure (2–4%). The mechanisms of T cardiotoxicity are not entirely known and can include changes in Ca²⁺ regulation related to blockade of ErbB2. Here, we aim at assessing whether ranolazine (RAN), diminishing intracellular Ca²⁺ through its inhibition of late Ina, blunts T cardiotoxicity in vivo.

Methods: To evaluate cardiac function in vivo, fractional shortening (FS) and ejection fraction (EF) were measured by echocardiography M-Mode in C57BL6 mice, 2-4 mo old, pretreated with RAN (750mg/kg/day, a dose comparable to the one used in humans) per os for 3 days. RAN was then administered for additional 7 days, alone and together with T (2.25 mg/kg/day ip), according to our well established protocol.

Results: In our in vivo studies, after 7 days with T, FS decreased to 49 ± 1.5%, p < 0.01 vs 60 ± 0.5% (sham), and EF to 81 ± 2%, p < 0.01 vs 91 ± 1% (sham). RAN alone did not change FS (59 ± 2%) nor EF 89 ± 1%. Interestingly, in mice treated with RAN and T, RAN prevents the reduction of EF and FS vs T alone (FS was 58 ± 1%, EF was 90 ± 1%, p = 0.01 and p < 0.01 respectively).

Conclusions: In our mouse model, T produces LV dysfunction and RAN blunts T cardiotoxic effects. We plan to test RAN as a cardioprotective agent with other target-therapy drugs in our experimental models and to define the mechanisms of cardioprotection.

Disclosure: All authors have declared no conflicts of interest.