BACKGROUND
Targeted therapies in cancer aim to block specific molecular pathways that are constitutively activated and are crucial for tumor cell growth and survival, but they also elicit immune responses. This raises the possibility that these treatments may be combined with immunotherapy to induce synergistic anti-tumor effects that improve treatment outcomes. How to rationally prioritize combinations of targeted agents with immunotherapies among the many possible options, represents a major unmet need in clinical oncology.

METHODS
We have developed a novel in situ approach that provides a phenotypic measurement of single and combinatorial drug effect directly within the tumors of patients or animal models. The approach uses implantable microdevices (IMD), which are loaded with nano-doses of up to 20 approved and experimental agents, and releases these treatments into confined and non-overlapping regions of the tumor where each treatment interacts with the native tumor microenvironment (TME) for multiple days. Upon retrieval of the IMD with surrounding tissue, a spatial analysis tissue phenotyping pipeline is employed to define the effect of each treatment on tumor and TME cells. For each treatment, a specific response and resistance phenotype is described which leads to the identification of an immune-modulating agent which combines synergistically with the targeted therapy.

RESULTS
We have employed this combined IMD - spatial analysis platform to identify three novel and highly synergistic combinations in breast cancer models, including inhibitors of CDK4/6, HDAC and BCL-2, as well as anti-PD1, anti-CSF1R and anti-CD40 treatments.

CONCLUSIONS
The approach is currently being used in multiple clinical studies, which provides a platform for validating the biomarkers and resistance signatures in patients.

REFERENCES

ETHICS APPROVAL
The study has obtained the required ethics approvals.