

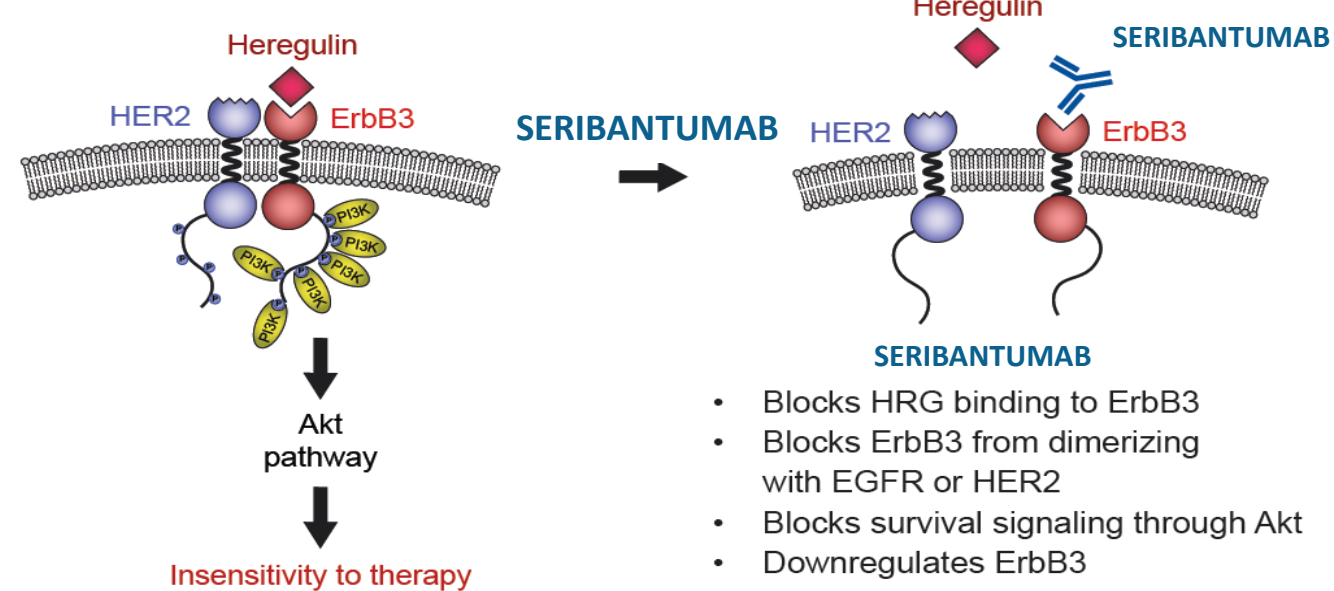


ErbB3 targeting drug seribantumab

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Merrimack Pharmaceuticals, Inc.

INTRODUCTION

Heregulin (HRG)-driven ErbB3 signaling mediates insensitivity to standard-of-care (SOC) cancer therapies in a variety of preclinical models. It is hypothesized that one way in which cancers become insensitive to therapy is by upregulating HRG-driven signaling through the ErbB3/PI3K/Akt pathway. Seribantumab (MM-121) is a fully human IgG2 antibody that binds to ErbB3 and blocks HRG from binding. In this way, seribantumab prevents ErbB3 from dimerizing with EGFR or HER2 and activating survival signaling. By blocking this pathway, it is hypothesized that seribantumab could restore sensitivity to therapy in tumors where this pathway is active.

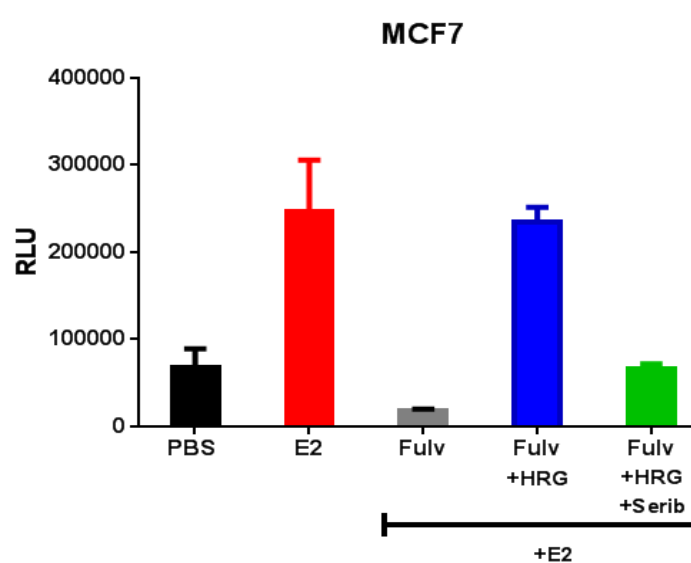


- Blocks HRG binding to ErbB3
- Blocks ErbB3 from dimerizing with EGFR or HER2
- Blocks survival signaling through Akt
- Downregulates ErbB3

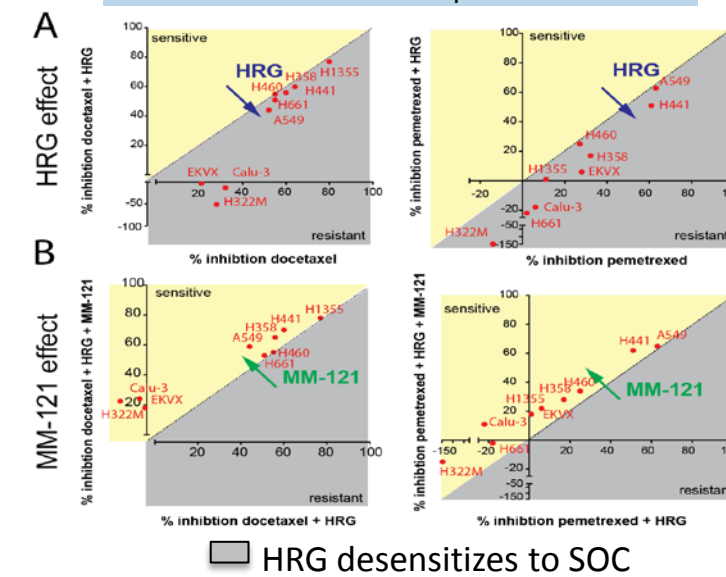
PRE-CLINICAL AND CLINICAL BACKGROUND

Pre-Clinical Data

HRG blocks and seribantumab increases sensitivity to fulvestrant in MCF7 cell lines

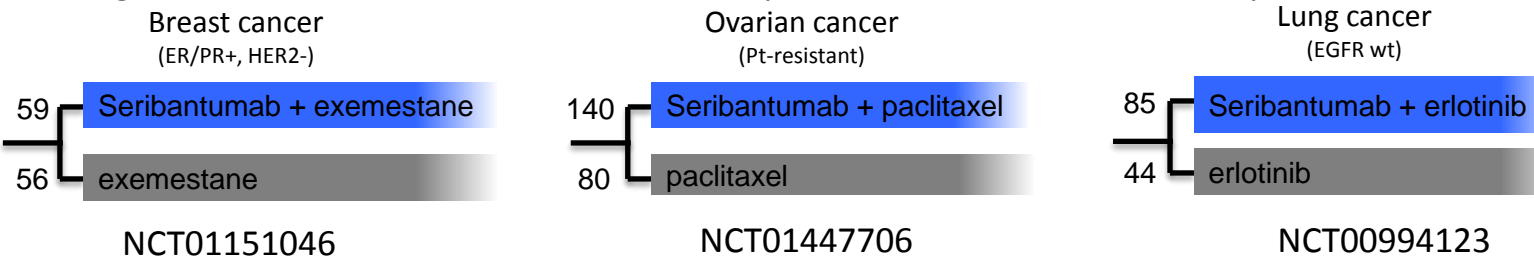


HRG blocks activity of multiple chemotherapies



Clinical Trials

Archived and fresh tissue was collected from patients participating in 3 randomized phase 2 trials examining seribantumab + standard of care therapies vs. standard of care therapies alone.



Assays

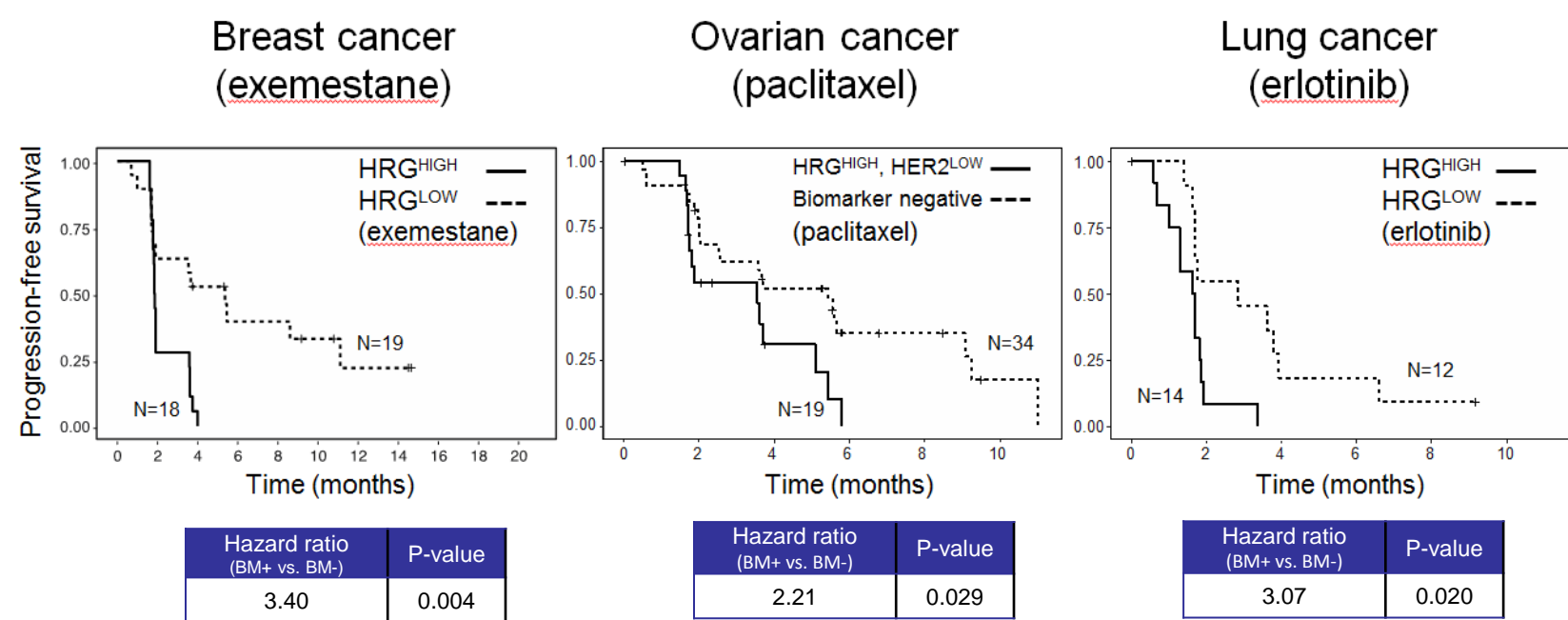
Biomarker	Fl-qIHC (protein)	Chr-IHC (protein)	RNA-ISH (mRNA)	RT-qPCR (mRNA)
EGFR	✓			✓
ErbB2	✓	✓		✓
ErbB3	✓	✓	✓	✓
HRG			✓	✓
BTC			✓	✓

✓ Discrete
 ✓ Continuous
 Fl-qIHC: Fluorescence-based quantitative immunohistochemistry
 Chr-IHC: Chromogenic-based immunohistochemistry
 RNA-ISH: RNA-based *in situ* hybridization
 RT-qPCR: Reverse transcription quantitative polymerase chain reaction

CLINICAL DATA: PHASE 2 BIOMARKER RESULTS

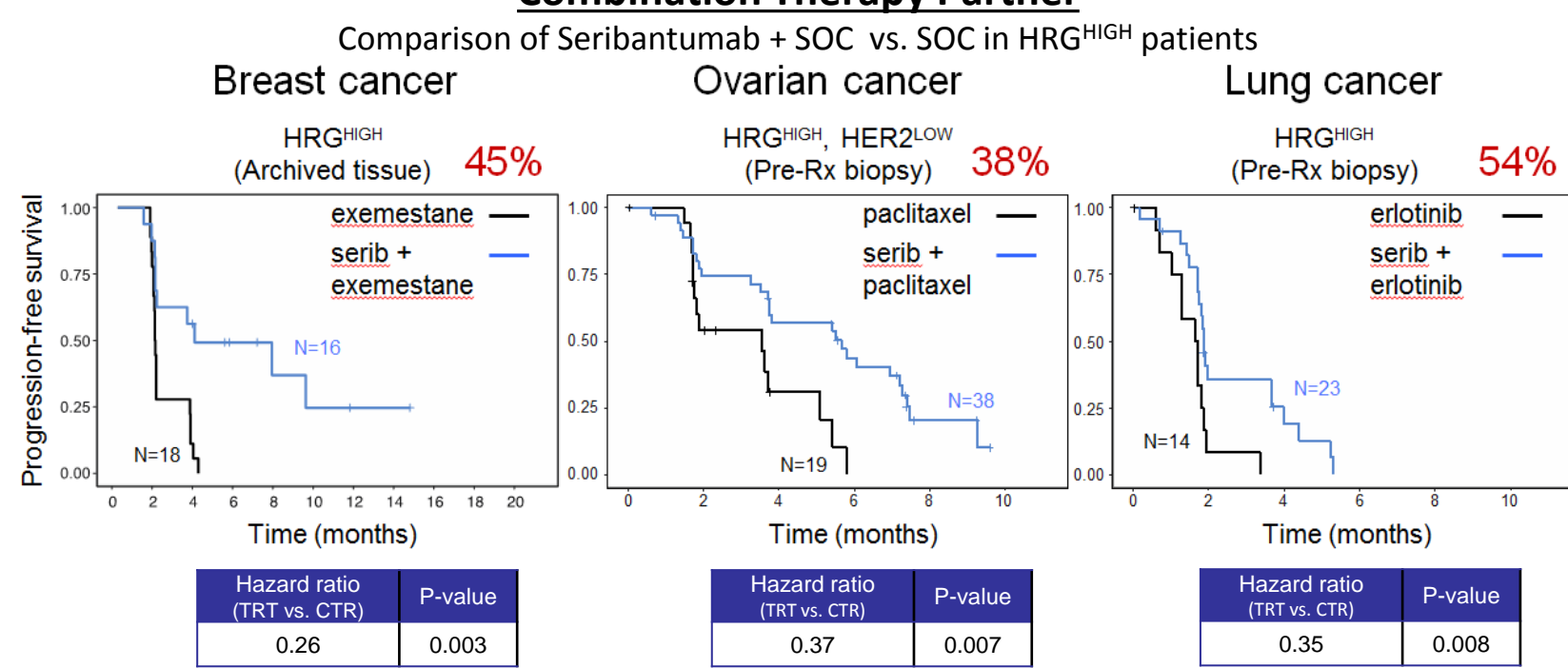
Heregulin Appears Prognostic of Shorter PFS on Standard Therapies

Comparison of PFS in HRG^{HIGH} vs HRG^{LOW} patients receiving standard-of-care therapy (control arm)



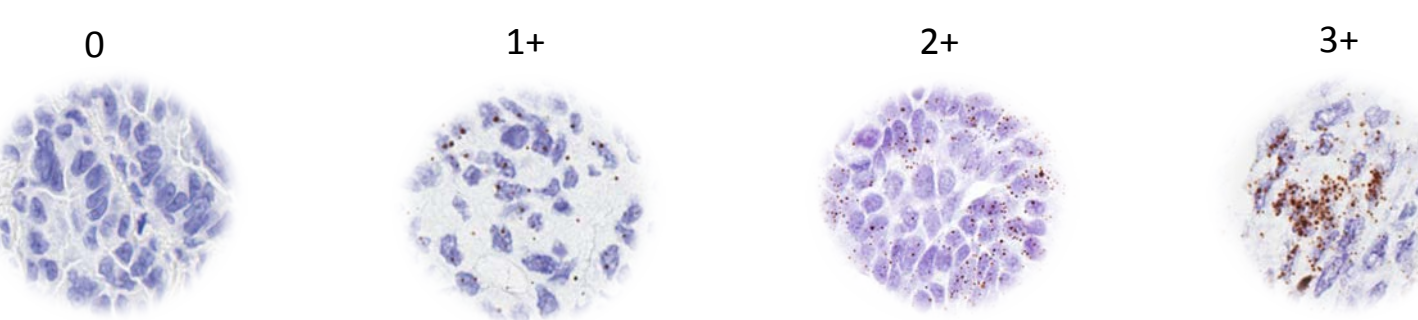
Blocking HRG Signaling with Seribantumab May Improve Anti-Tumor Effect of Combination Therapy Partner

Comparison of Seribantumab + SOC vs. SOC in HRG^{HIGH} patients

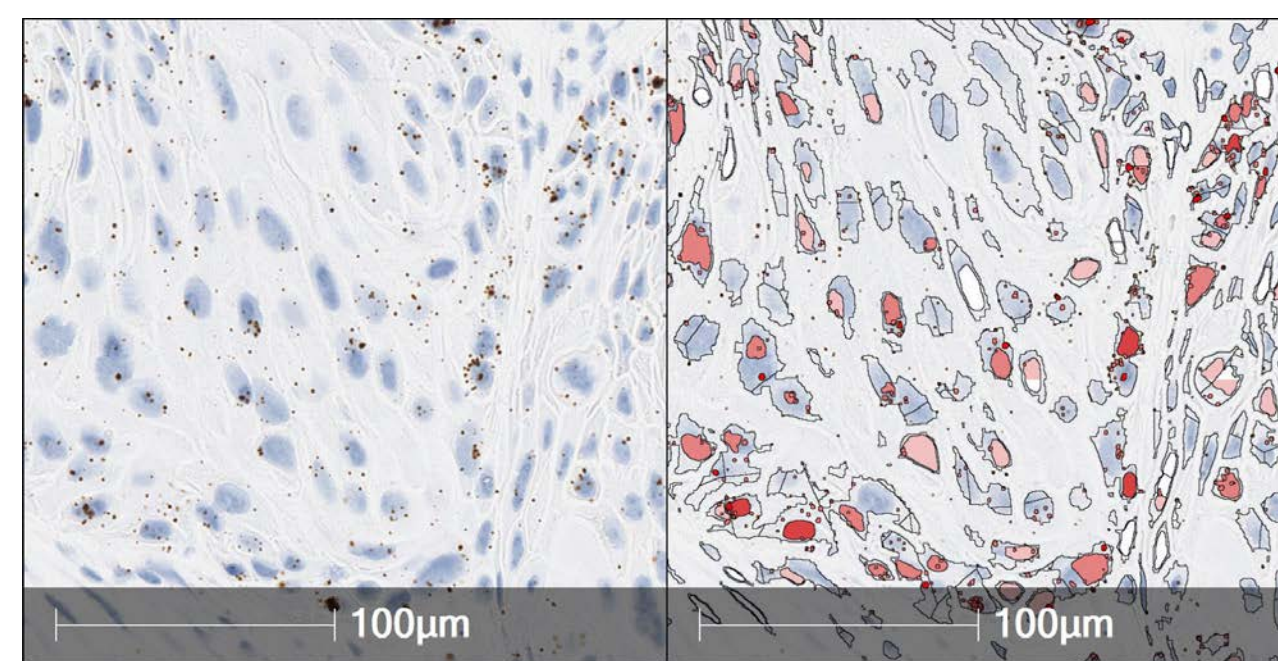


HRG mRNA SCORING

Pathologist Scoring by ISH



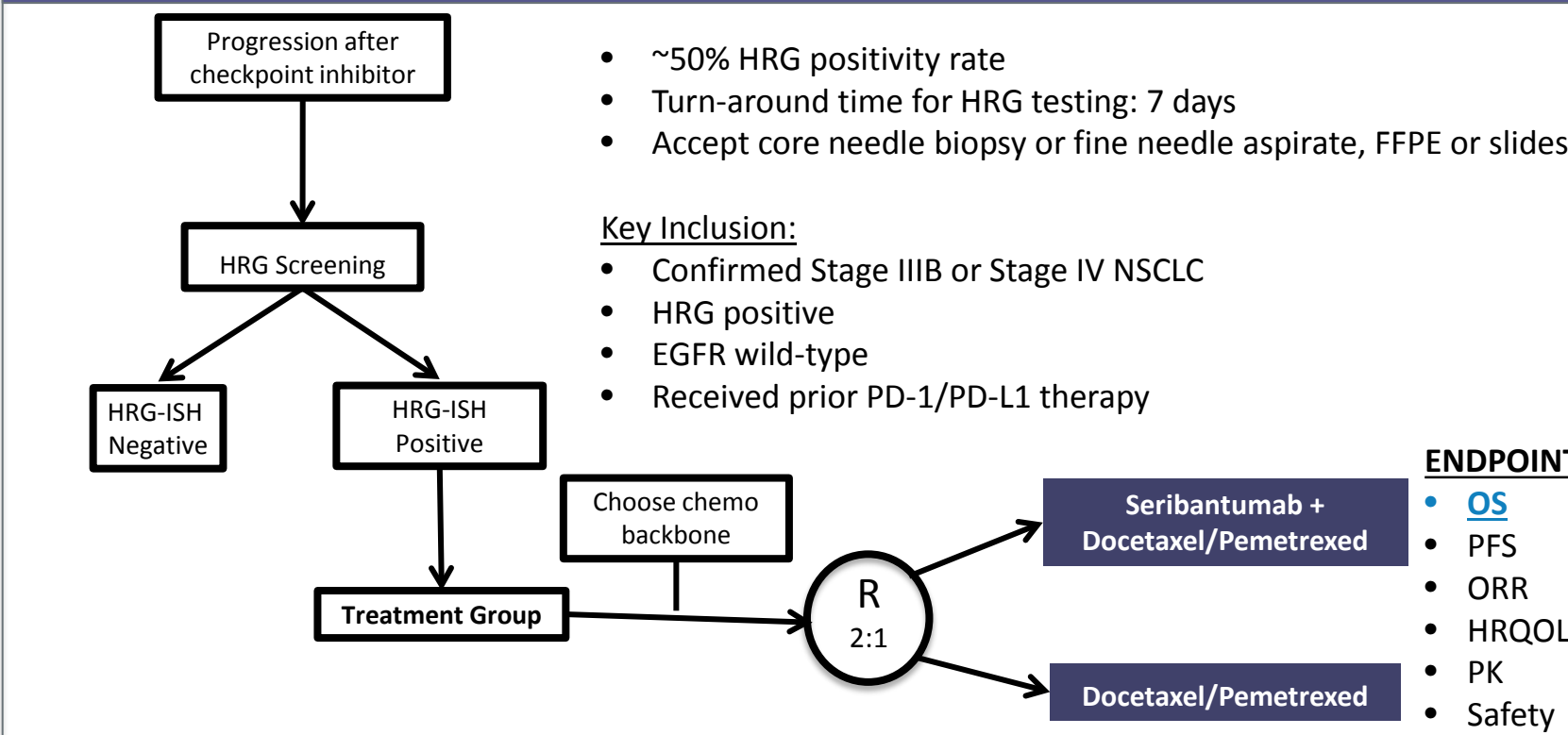
Digital Pathology



- Digital analysis performed using "Halo" software (Indica Labs)
- Demonstrated high concordance (>80%) with manual pathologist scoring in NSCLC samples.

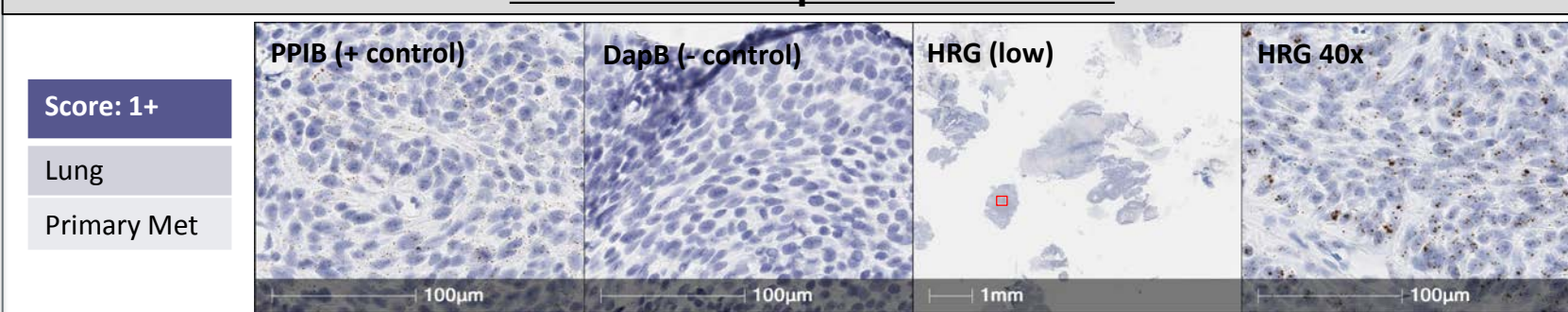
Score
0 (white)
1+ (light pink)
2+ (pink)
3+ (dark pink)
4+ (red)

ONGOING CLINICAL TRIAL (NCT02387216)

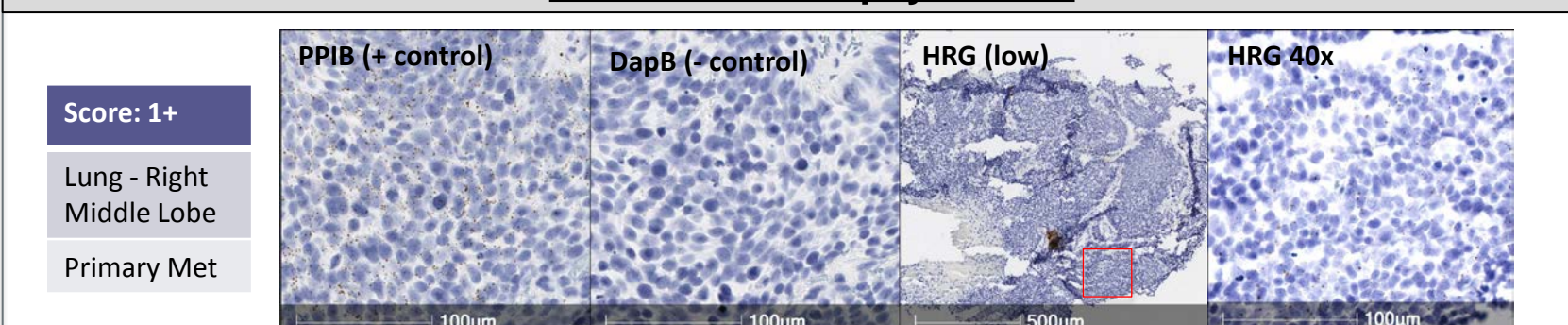


CLINICAL SAMPLES

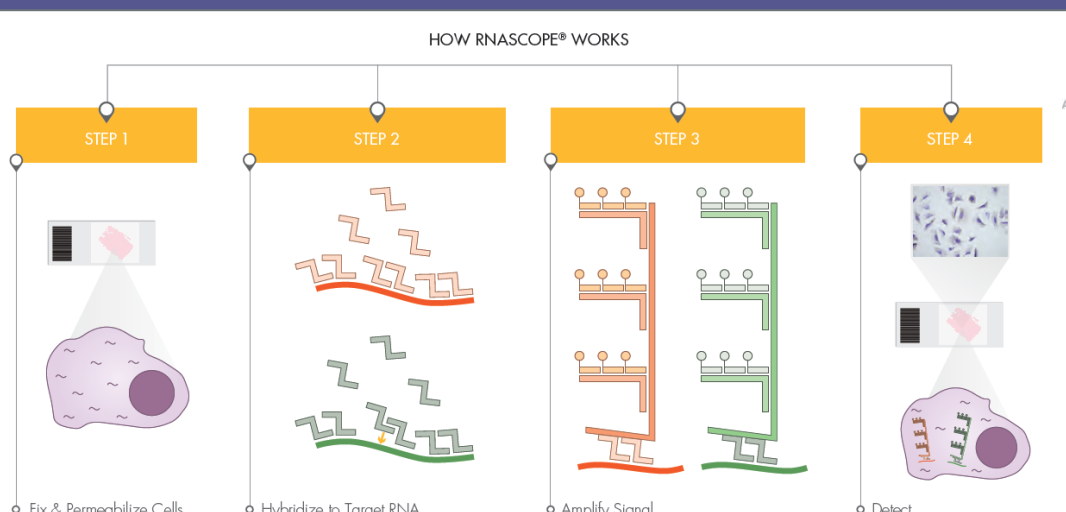
Fine Needle Aspirate - Archived



Core Needle Biopsy - Fresh



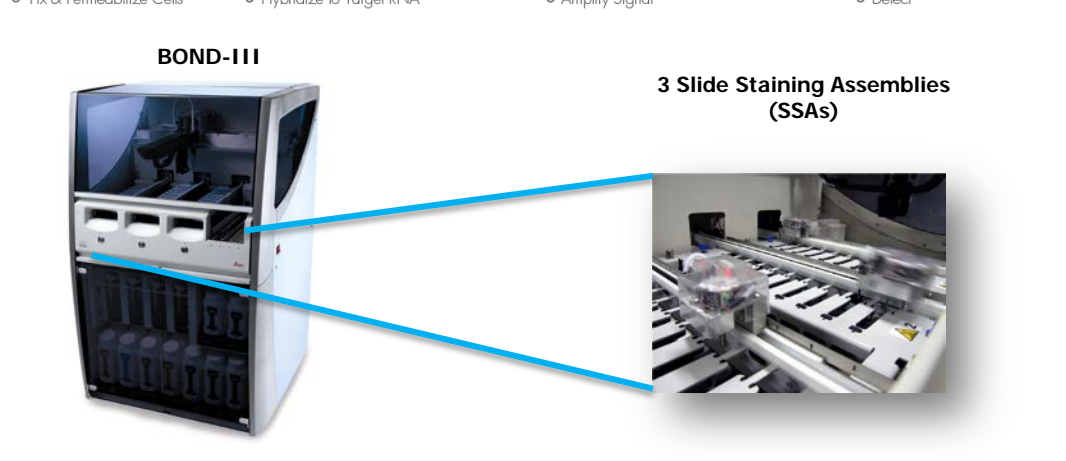
HEREGULIN RNA-ISH ASSAY



HOW RNASCOPE® WORKS

ACD
ADVANCED CELL DIAGNOSTICS, INC.

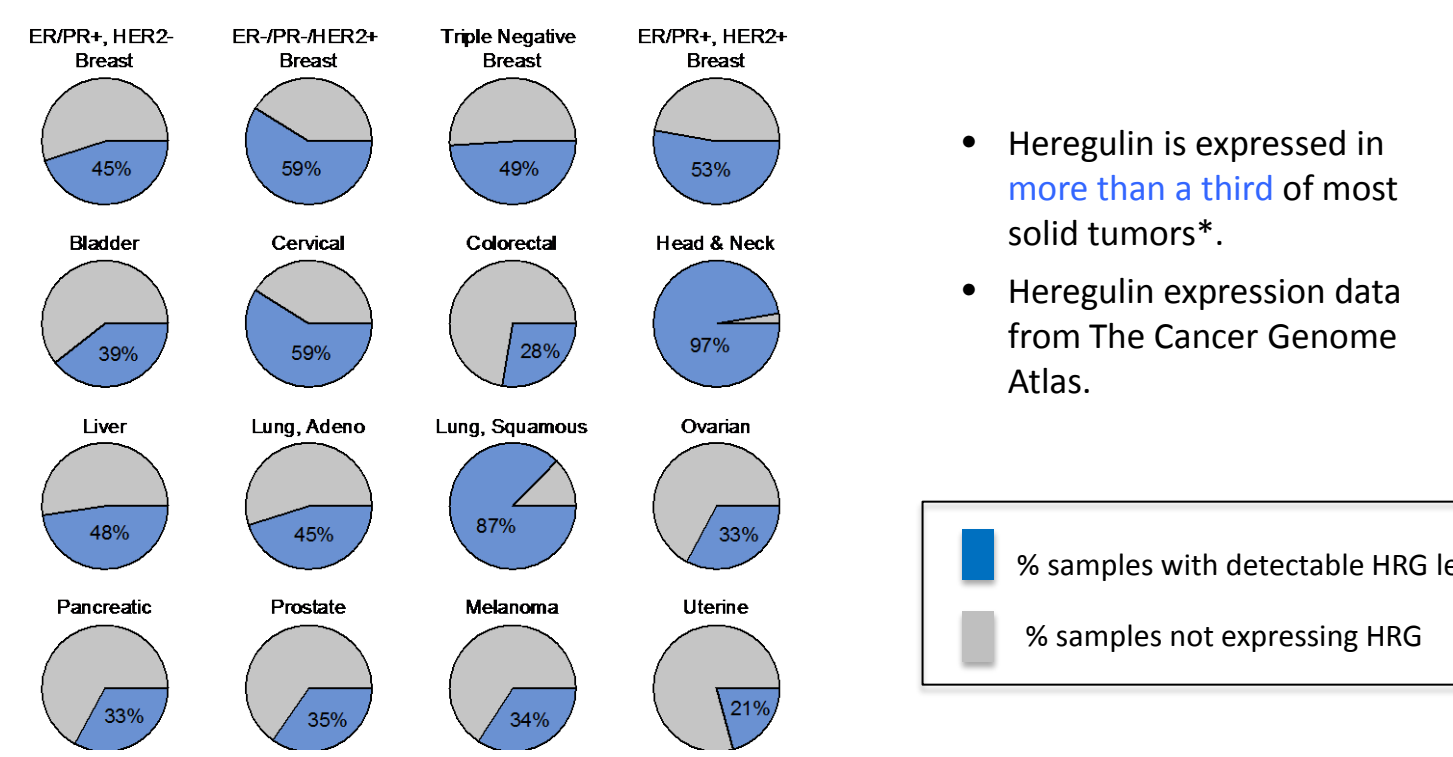
- Assay technology developed by Advanced Cell Diagnostics (ACD)
- Clinical HRG assay optimized by Merrimack



- Fully automated assay to be run on Leica's auto-stainer
- Amenable to many sample types
 - Core needle biopsies
 - Fine needle aspirates
 - Surgical resections
- Independent pathologist scored

HEREGULIN IS WIDELY EXPRESSED

Heregulin is broadly expressed across multiple tumor types



SUMMARY

- The addition of seribantumab to standard of care therapies has the potential for substantial benefit for patients with HRG positive tumors
- HRG is detected at significant levels across multiple solid tumor types with a prevalence between 30-60%
- RNA-ISH is an optimal platform to measure HRG mRNA expression in tumor cell tissue
- A fully validated RNA-ISH assay currently in use in a Phase 2 randomized trial and is successfully identifying HRG positive NSCLC patients

NEXT STEPS:

- Further implement assay in new indications in upcoming clinical trials
- Merrimack and Leica Biosystems to collaborate on developing diagnostic kit for commercial use, using Advanced Cell Diagnostics' (ACD's) RNAscope technology and processing on Leica Biosystems' BOND clinical advanced staining systems