A Randomized Trial of Exemestane +/- Seribantumab (MM-121) in Postmenopausal Women With Locally Advanced or Metastatic ER/PR+ HER2- Breast Cancer: Final Analysis and Extended Subgroup Analysis.

Abstract #

Greg Finn[1], Hong Zhang[1], Anna Blois[1], Sara Mathews[1],Art Kudla[1], Jason Baum[1], Mike Cieslewicz[1], Birgit Schoeberl[1], Gavin Macbeath[1] , Bambang Adiwijaya[1] and Akos Czibere[1]

[1] Merrimack Pharmaceuticals, Inc., Cambridge, MA., USA

Introduction

ErbB3 is a member of the ErbB family of growth factor receptors which comprises four receptors (ErbB1-4). ErbB2 lacks the capacity to interact with the growth-factor ligand, whereas the kinase activity of ErbB3 is defective. ErbB2 and ErbB3 form heterodimeric complexes with other ErbB receptors that are capable of generating potent cellular signals including MAPK and PI3K/AKT that are known to play a role in cancer.

- Heregulin (HRG) is the cognate ligand for ErbB3 and marks a distinct tumor phenotype
- HRG is widely expressed in tumors including ER+ HER2- breast cancer
- HRG mediates resistance to multiple SOC therapies including anti-hormonal therapies such as SERDs & aromatase inhibitors (AI)
- Loss of responsiveness to anti-hormonal therapies is a significant clinical challenge for patients with ER+/PgR+, HER2- metastatic breast cancer (mBC)
- Seribantumab is a fully human anti-ErbB3 mAb that blocks HRG binding to ErbB3 to inhibit downstream signaling

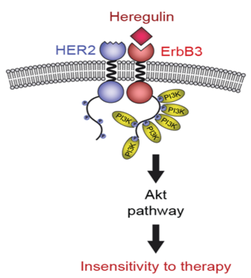
Clinical results from a randomized, Phase 2 study in women with metastatic breast cancer who received seribantumab plus exemestane or placebo plus exemestane highlighted the ability to sensitize HRG-positive tumors to exemestane by co-administration with seribantumab. Findings from the Phase 2 include:

- HRG is a biomarker for seribantumab response and is prognostic for poor performance on SOC anti-hormonal therapy
- Seribantumab removes the negative prognostic effects of HRG in patients with HRG+ tumors
- Patients who progressed in the metastatic setting derived the most benefit from adding seribantumab to exemestane for mBC
- Seribantumab is well tolerated in combination with exemestane

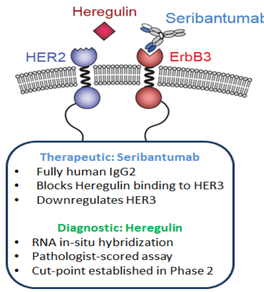
Results suggest that HRG+ patients with mBC may benefit from the addition of seribantumab to their anti-hormonal treatment program.

Seribantumab (MM-121): Mechanism Of Action

HER3-HRG Drives Tumor Resistance



Seribantumab displaces HRG from HER3

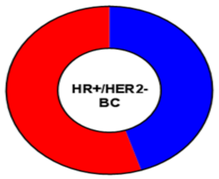


Therapeutic: Seribantumab
- Fully human IgG2
- Blocks Heregulin binding to HER3
- Downregulates HER3

Diagnostic: Heregulin
- RNA in-situ hybridization
- Pathologist-scored assay
- Cut-point established in Phase 2

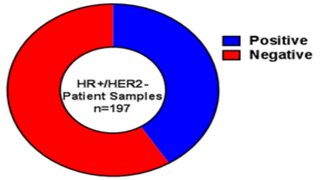
HRG Prevalence in HR+, HER2- Breast Cancer

HRG mRNA in HR+, HER2- breast cancer from TCGA database



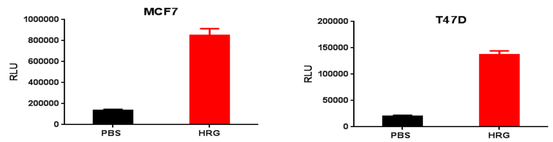
HRG+ 45%

HRG mRNA in HR+, HER2- breast cancer patient samples measured by HRG-RNA-ISH

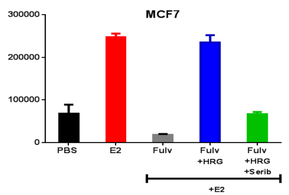


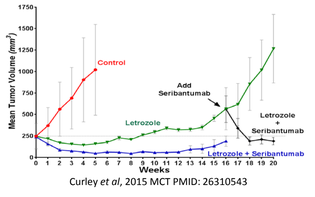
- TCGA database HRG mRNA prevalence rate concurs with rates determined by direct measurement of HRG in HR+, HER2- patient tumor samples by RNA-ISH assay
- Data demonstrates that ~45% of HR+, HER2- breast cancer patients are HRG-positive

HRG Inhibits Activity of Endocrine Therapy in HR+, HER2- Breast Cancer Models



- HRG drives direct proliferation of HR+ cell lines

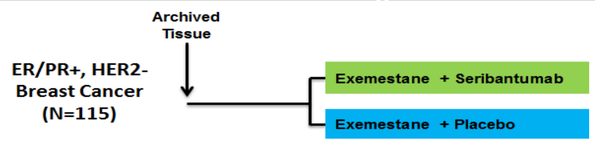




Curley *et al*, 2015 MCT PMID: 26310543

- HRG inhibits the activity of fulvestrant in HR+ cells
- Seribantumab blockade of ErbB3 restores activity of fulvestrant
- Seribantumab blockade of ErbB3 restores sensitivity to letrozole and blocks onset of letrozole resistance in an *in vivo HR+ HER2-* aromatase driven model

Seribantumab Phase 2 Trial in HR+, HER2- Breast Cancer: Trial Design



Randomized, placebo-controlled Phase 2 trial

Inclusion Criteria
- ER+/PR+, HER-2 negative, locally advanced or metastatic breast cancer.
- Post-menopausal women who progressed following prior anti-hormonal therapy
- Archived tissue sample for biomarker analysis

Exclusion Criteria
- Prior exemestane exposure
- Extensive visceral disease

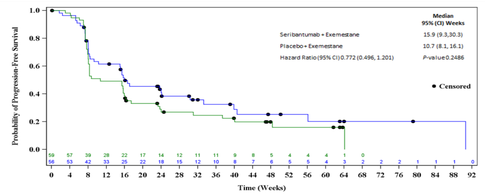
Seribantumab Phase 2 Trial in HR+, HER2- Breast Cancer: Safety

Summary of All Adverse Events

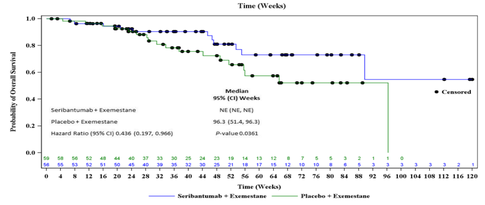
	Seribantumab + Exemestane N = 56	Placebo + Exemestane N = 59
Subjects with at least one AE	48 (85.7)	51 (86.4)
Subjects with at least one TEAE	48 (85.7)	50 (84.7)
Subjects with CTCAE grade 3 or higher TEAE	14 (25.0)	15 (25.4)
Subjects with TEAE related to study drug (a)	40 (71.4)	32 (54.2)
Subjects with serious TEAE	7 (12.5)	11 (18.6)
Subjects with TEAE leading to death	2 (3.6)	1 (1.7)
Subjects with TEAE leading to dose discontinuation	2 (3.6)	0

- No difference in any grade or grade 3 or higher incidence of TEAEs
- No difference in serious TEAEs
- All fatal AEs were disease progression-related
- Overall well tolerated combination of Seribantumab & Exemestane

Efficacy in ITT Population

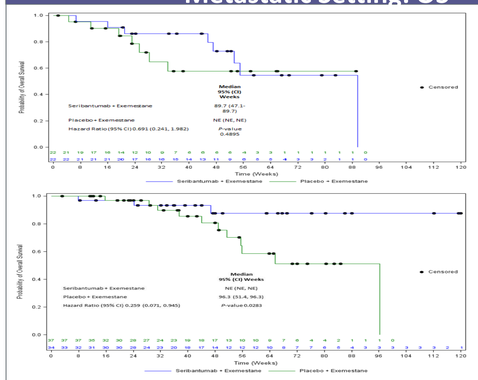


Primary Endpoint: PFS in ITT Population



Secondary Endpoint: OS in ITT Population

Progression in the Adjuvant Setting vs the Metastatic Setting: OS

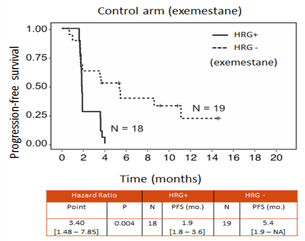


OS in patients who progressed in the adjuvant setting prior to entering study

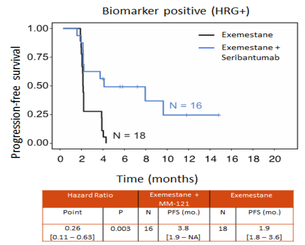
OS in patients who progressed in the metastatic setting prior to entering study

The authors thank colleagues at Merrimack Pharmaceuticals for helpful discussions and support during the preparation of this work

HRG mRNA is Prognostic of Poor Performance on SOC & Seribantumab Restores Activity of Exemestane in HR+ mBC Patients



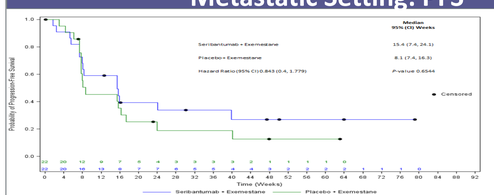
Hazard Ratio		HRG+		HRG -	
Point	P	N	PFS (mo.)	N	PFS (mo.)
3.40 [1.48 – 7.85]	0.004	18	1.9 [1.8 – 3.6]	19	5.4 [1.9 – NA]



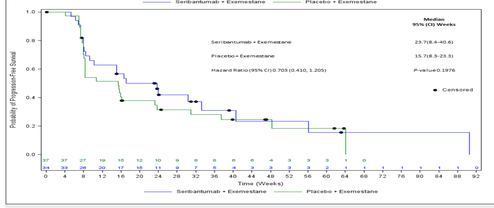
Hazard Ratio		Exemestane + MM-121		Exemestane	
Point	P	N	PFS (mo.)	N	PFS (mo.)
0.26 [0.11 – 0.63]	0.003	16	3.8 [1.9 – NA]	18	1.9 [1.8 – 3.6]

- Patients with HRG+ tumors progressed faster on exemestane than patients who had HRG- tumors
- Seribantumab restores activity of exemestane in HRG+ mBC patients

Progression in the Adjuvant Setting vs the Metastatic Setting: PFS



PFS in patients who progressed in the adjuvant setting prior to entering study

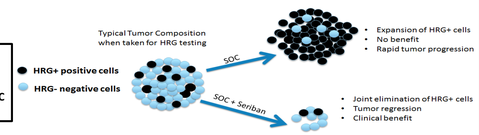


PFS in patients who progressed in the metastatic setting prior to entering study

Summary & Conclusions

- Loss of sensitivity to endocrine based therapies in HR+, HER2- breast cancer is a significant clinical challenge
- HR+, HER2- mBC patients who progress on endocrine therapies would benefit a well tolerated and active therapy to delay cytotoxic chemo use.
- HRG in tumors marks a distinct cancer phenotype

HRG protects cells from therapy promoting clonal evolution of resistant populations and failure of SOC regimens



- Seribantumab in combination with endocrine blockade decreased the risk of death to HR+, HER2- mBC patients
- Greatest benefit was seen in patients who progressed in the metastatic setting prior to receiving seribantumab
- Seribantumab should be tested in combination with endocrine therapies for HR+, HER2-, HRG+ mBC patients in a Phase 3 trial