

Supplementary Information

Safety and efficacy of neoadjuvant HSP90 inhibitor ganetespib in stage II/III breast cancer in the adaptively randomized I-SPY2 trial

Lang JE, et al.

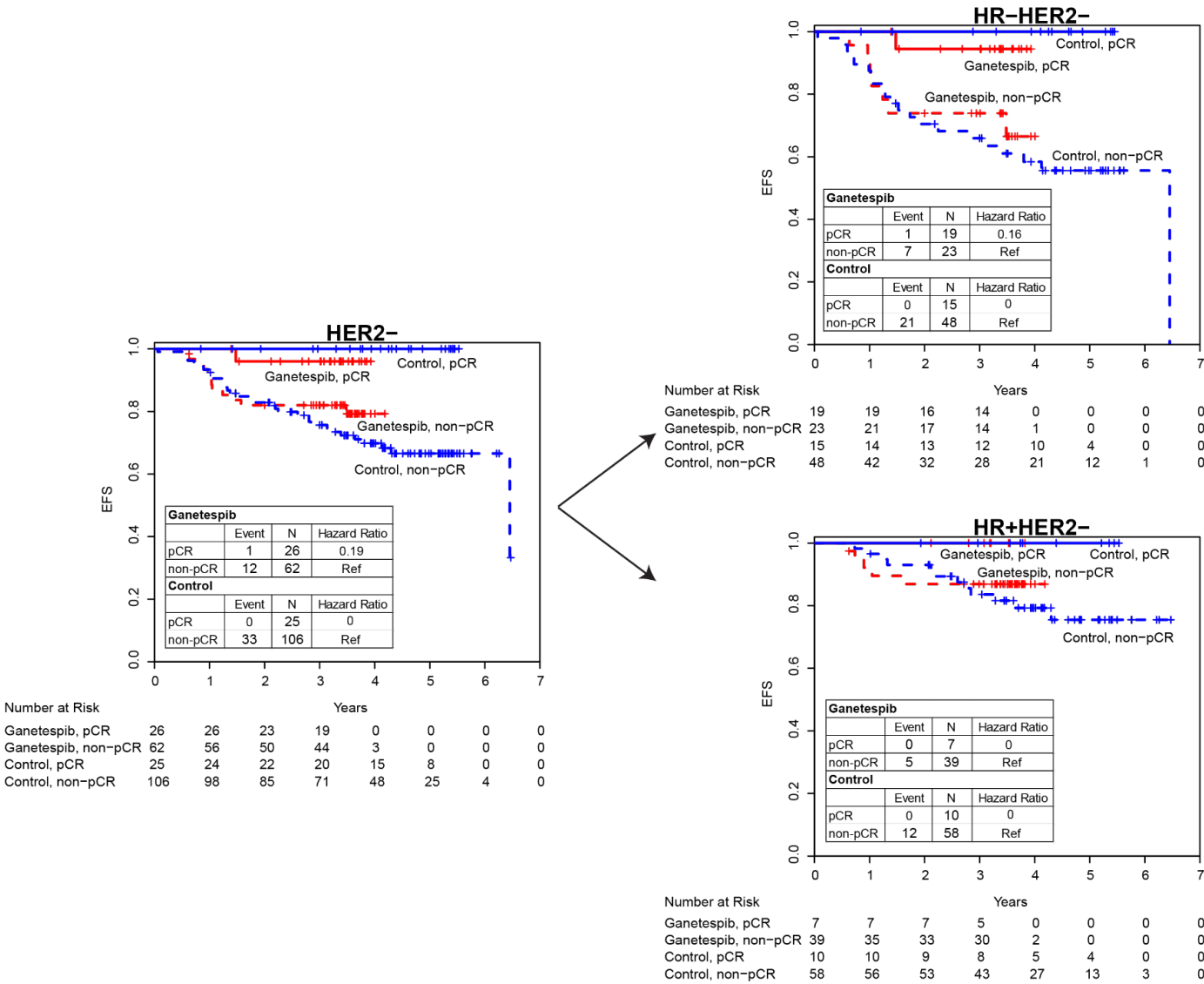
Supplementary Table 1: Final predictive probabilities of success of ganetespib with paclitaxel followed by anthracyclines in HER2-signatures.

Biomarker Signature	Estimated Rate of pCR % (95% Probability Interval)		Prob. Superior to Control, %	Predictive Prob. of Success in Phase III Trial, %
	ganetespib n=93	control n=140		
HER2-	26 (16 - 37)	18 (8 – 28)	91	47
HR- HER2-	38 (23 - 53)	22 (9 - 35)	96	72
HR+ HER2-	15 (4 - 27)	14 (4 - 24)	60	19

Supplementary Table 2: Association of prespecified biomarkers with pCR in overall population and HR-negative/HR-negative (TN, triple negative) and HR-positive/HER2-negative subtypes.

Biomarker	Overall Population					TN subset					HR+HER2-				
	Ganetespi b arm		Control arm		Biomarker x treatment int: LR p	Ganetespi b arm		Control arm		Biomarker x treatment int: LR p	Ganetespi b arm		Control arm		Biomarker x treatment int: LR p
	OR/unit inc	LR p	OR/unit inc	LR p		OR/unit inc	LR p	OR/unit inc	LR p		OR/unit inc	LR p			
HSP90; single gene															
HSP90AA1	1.02	0.934	0.932	0.752	0.78	0.728	0.376	0.958	0.891	0.569	1.02	0.953	0.904	0.758	0.81
HSP90AB1	1.59	0.074	0.861	0.5	0.0719	1.37	0.285	0.623	0.0848	0.0517	2.38	0.14	1.79	0.168	0.707
HSP90B1	0.985	0.942	1.11	0.67	0.71	0.718	0.25	0.819	0.616	0.788	1.03	0.939	1.24	0.536	0.726
TRAP1	1.46	0.211	1.07	0.748	0.401	1.49	0.314	0.848	0.562	0.248	1.1	0.861	1.42	0.279	0.692
DNAJB1	0.686	0.158	0.955	0.827	0.337	0.83	0.596	0.871	0.614	0.914	0.621	0.347	1.14	0.692	0.318
HSPA1A	0.842	0.434	0.897	0.634	0.841	1.03	0.909	1.62	0.193	0.34	1.08	0.873	0.627	0.165	0.342
HSPA1L	0.854	0.58	0.554	0.00772	0.242	1.23	0.555	0.519	0.0503	0.0791	0.697	0.533	0.618	0.123	0.858
HSPA4	0.901	0.665	0.796	0.306	0.707	0.672	0.175	0.582	0.101	0.755	1.11	0.834	1.19	0.601	0.91
STIP1	1.08	0.775	1.5	0.0713	0.356	0.881	0.725	1.14	0.651	0.576	1.63	0.332	2.22	0.0276	0.627
CDC37	0.869	0.63	1.46	0.0794	0.152	0.975	0.952	1.18	0.578	0.712	0.793	0.654	1.79	0.08	0.176
GR/efflux; single gene															
UGT1A6	1.07	0.762	0.72	0.203	0.27	1.13	0.65	0.657	0.251	0.24	0.879	0.825	0.823	0.587	0.927
UGT1A8	0.879	0.642	0.72	0.161	0.601	0.942	0.839	0.633	0.225	0.417	0.605	0.451	0.84	0.573	0.664
NR3C1	0.867	0.572	0.929	0.742	0.837	1.2	0.563	0.98	0.943	0.634	0.325	0.04	0.828	0.594	0.163
HSP90 ratio															
HSP90_HSP70_ratio1	1.18	0.456	1.06	0.798	0.745	0.866	0.646	0.677	0.257	0.603	0.953	0.912	1.47	0.258	0.423
HSP90_HSP70_ratio2	1.42	0.0923	0.979	0.927	0.232	1.18	0.537	0.349	0.00686	0.0116	1.31	0.496	2.71	0.0142	0.2
Immune signature															
Llexpression_score	1.58	0.0761	1.7	0.0141	0.84	1.27	0.435	1.36	0.292	0.883	1.78	0.278	2.12	0.0284	0.785
Replicative stress (proliferation) signature															
Module11_Prolif_score	1.43	0.115	1.45	0.131	0.976	0.586	0.237	1.02	0.947	0.331	1.47	0.33	1.84	0.104	0.694
PARPi7_score	1.26	0.351	1.42	0.112	0.719	0.87	0.654	1.28	0.43	0.381	1.61	0.364	1.42	0.361	0.844

Supplementary Figure 1: Kaplan Meier lots of event-free survival in ganetespiib and control arms, displayed by post-surgical pCR status in: (A) all HER2-negative participants; (B) triple negative participants; (C) HR-positive/HER2-negative participants.



Supplementary Figure 2: Definition of MP1 and MP2 subtype. The figure depicts a heat map representation of the 70 genes in the MammaPrint score. The rows are the patients, and the columns are each of the 70 genes. The cut point of -0.154 for MP1 vs MP 2 is the midpoint of I-SPY 1 patient MammaPrint results that would have been eligible for I-SPY 2. The MP1 to MP2 threshold on the current commercially available MP test translates to -0.569, after an adjustment of the high versus low threshold to 0.00 (numerical subtraction of 0.415). The prevalence for each of the subtypes (as of August 2015) in the I-SPY 2 TRIAL is listed along the right hand border of the figure.

