

Expanded View Figures

Figure EV1. Information for patient cohorts from the BIMET-1 trial and from the University of Miami/Sylvester Comprehensive Cancer Center's umbrella biomarker protocol who were profiled in this study.

(A) Age, PSA levels and BMI for the patients ($n = 5$) in Arm A and patients ($n = 7$) in Arm B from the BIMET-1 trial. The patients in Arm B are further subdivided into responders, R (in red), or non-responders, NR. Positive response was defined as a decline in serum PSA. *One patient was categorized as a partial responder due to a rapid decrease in PSA for the first four weeks of metformin monotherapy but then followed by an increasing PSA. **Patient sera samples that were unavailable at the end of D225. (B) Trendlines showing changes in lactate at the D56 timepoint vs. D1 for individual Arm B patients from the BIMET-1 trial who were classified as metformin responders (R) or non-responders (NR). (C) Disease stage, age, BMI, PSA levels, and hormone therapy status for prostate cancer patients enrolled through an umbrella biomarker specimen collection protocol and profiled in this study for Lac-Phe levels in Fig. 1F. Source data are available online for this figure.

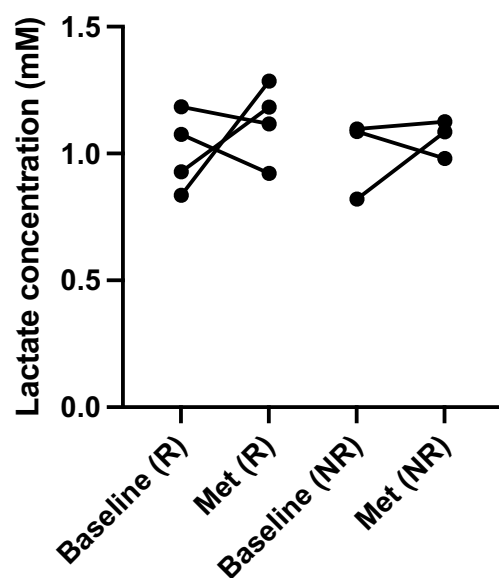
A

Patient ID	Days of blood collection	Age	Gleason	Baseline PSA	PSA (56d)	PSA (225d)	Arm	Met Response (PSA decline 56d)	BMI (baseline)	BMI (56d)	BMI (225d)
B-2	1, 56, 225	67	4+3=7	3.72	3.53	0.02	metformin	R	28.3	28.1	28.1
B-9	1, 56, 225	64	4+4=8	5.41	5.2	0.36	metformin	R	29.9	29.1	29.2
B-12	1, 56, 225	53	4+5=9	2.09	1.88	0.7	metformin	R	27.1	24.2	25.7
B-16*	1, 56	72	4+3=7	0.88	0.93	0.3	metformin	R*	28.4	28.3	25.8**
B-3	1, 56, 225	74	3+5=8	16.26	20.22	2.14	metformin	NR	25.6	25.4	26.3
B-14	1, 56, 225	58	4+5=9	4.07	5.1	0.14	metformin	NR	30.4	29.8	29.5
B-15	1, 56, 225	73	4+3=7	10.76	13.1	0.66	metformin	NR	25.9	25.4	25.1**
A-1	1, 56, 225	63	4+3=7	1.18	1.53	0.06	observation	NR	33.1	33.6	35
A-6	1, 56, 225	68	3+4=7	10.99	16.23	2.8	observation	NR	29.4	30.1	30
A-8	1, 56, 225	60	5+4=9	7.48	8.27	1.49	observation	NR	33.8	33.2	33.1
A-10	1, 56, 225	56	3+4=7	22.09	27.05	2.26	observation	NR	34	32.9	33
A-13	1, 56, 225	65	4+4=8	5.07	7.18	0.3	observation	NR	37.2	37.3	38.2

*partial responder - initial rapid decrease in PSA during the first four weeks, followed by an increase

**sera samples not available for profiling at this timepoint

B



C

Patient Characteristics (n=25)	No metabolism-modifying drugs (15 patients)	On metabolism-modifying drugs (10 patients)
Disease stage (% total patients)	mHSPC/BCR: 53.3% mCRPC: 46.7%	mHSPC/BCR: 60% mCRPC: 40%
Age (mean +/- SEM)	70.7 +/- 1.7	71 +/- 2.5
BMI (mean +/- SEM)	25.6 +/- 1.1	31.7 +/- 1.5
PSA (mean +/- SEM)	59.05 +/- 31.1	2.1 +/- 0.87
On ADT or ARSi	12/15 (80%)	8/10 (80%)
% of patients on metabolism-modifying drugs	n/a	Metformin: 70% Tirzepatide: 10% Insulin: 10% Semaglutide: 10%

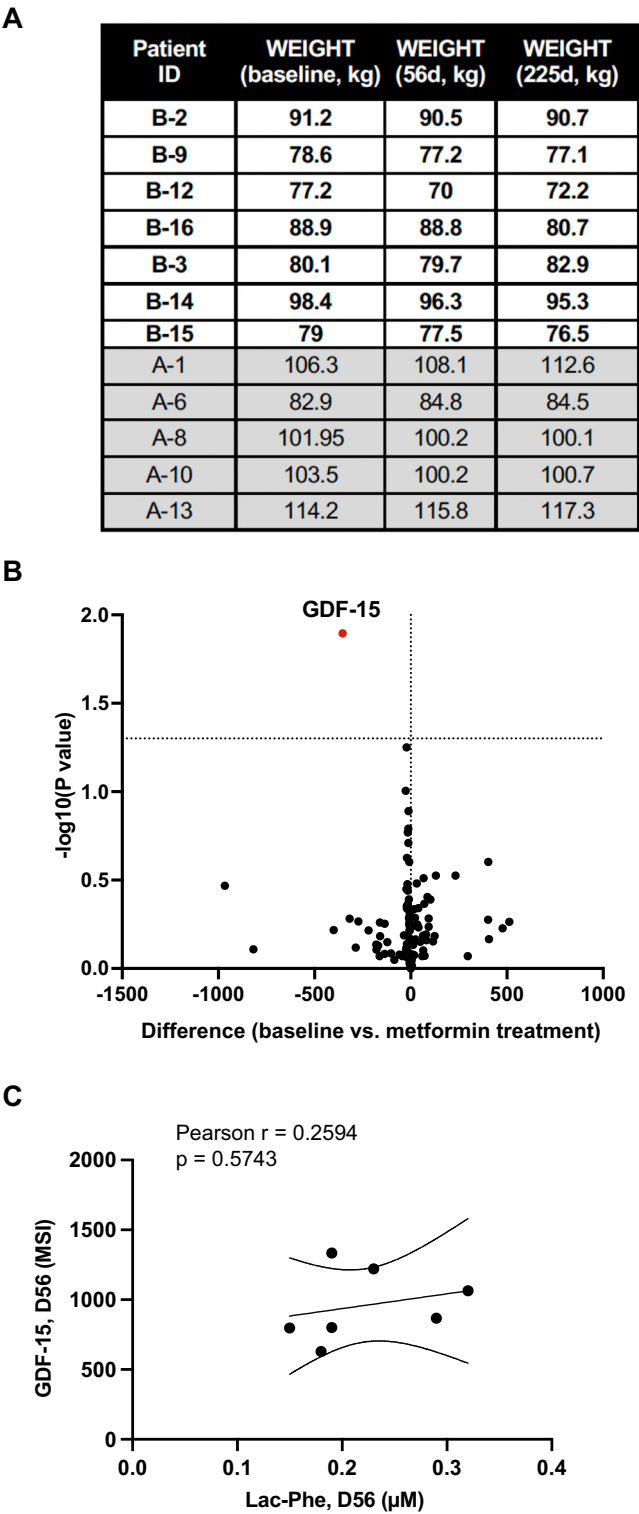


Figure EV2. GDF-15 is elevated by metformin treatment but does not significantly correlate with Lac-Phe levels.

(A) The weight of all patients ($n = 12$) at baseline (before treatment or observation), 2 months post-metformin treatment or observation (D56) and at the end of the trial (D225, including 6 months of metformin + bicalutamide, Met + Bic). (B) Volcano plot of significant changes in cytokine levels (mean signal intensity, MSI) following metformin monotherapy (D56), measured in Arm B patient sera. D56 values were compared to sera values at D1 and statistical significance determined via an unpaired Student's t test with Welch's correction for unequal variance. (C) Correlation between Lac-Phe levels (μM) vs. GDF-15 levels (MSI) at the D56 (metformin monotherapy) timepoint for Arm B patients. The linear regression line and 95% confidence intervals are shown, with Pearson correlation coefficient, r , and P value of the correlation noted above the graph. Source data are available online for this figure.