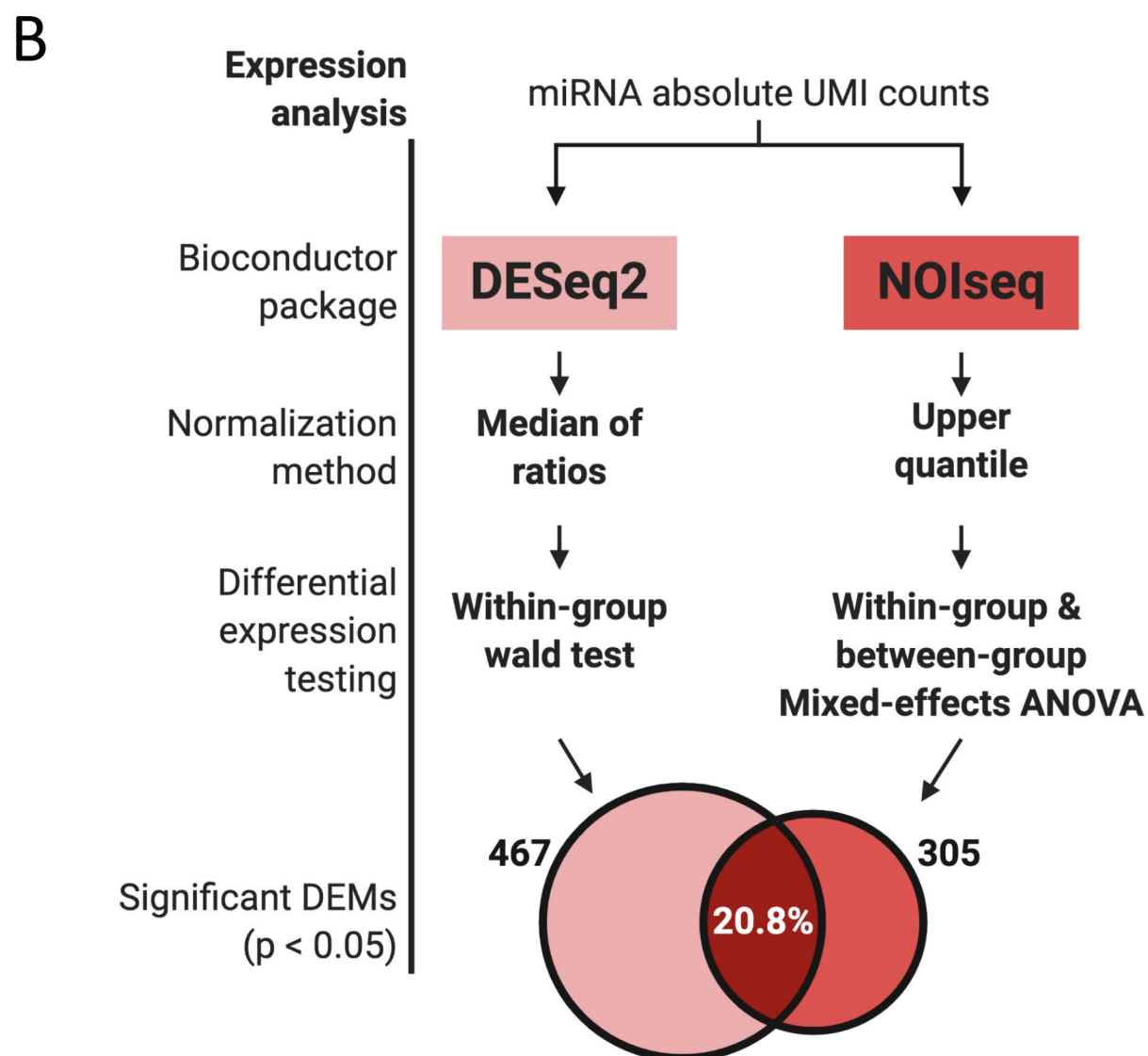
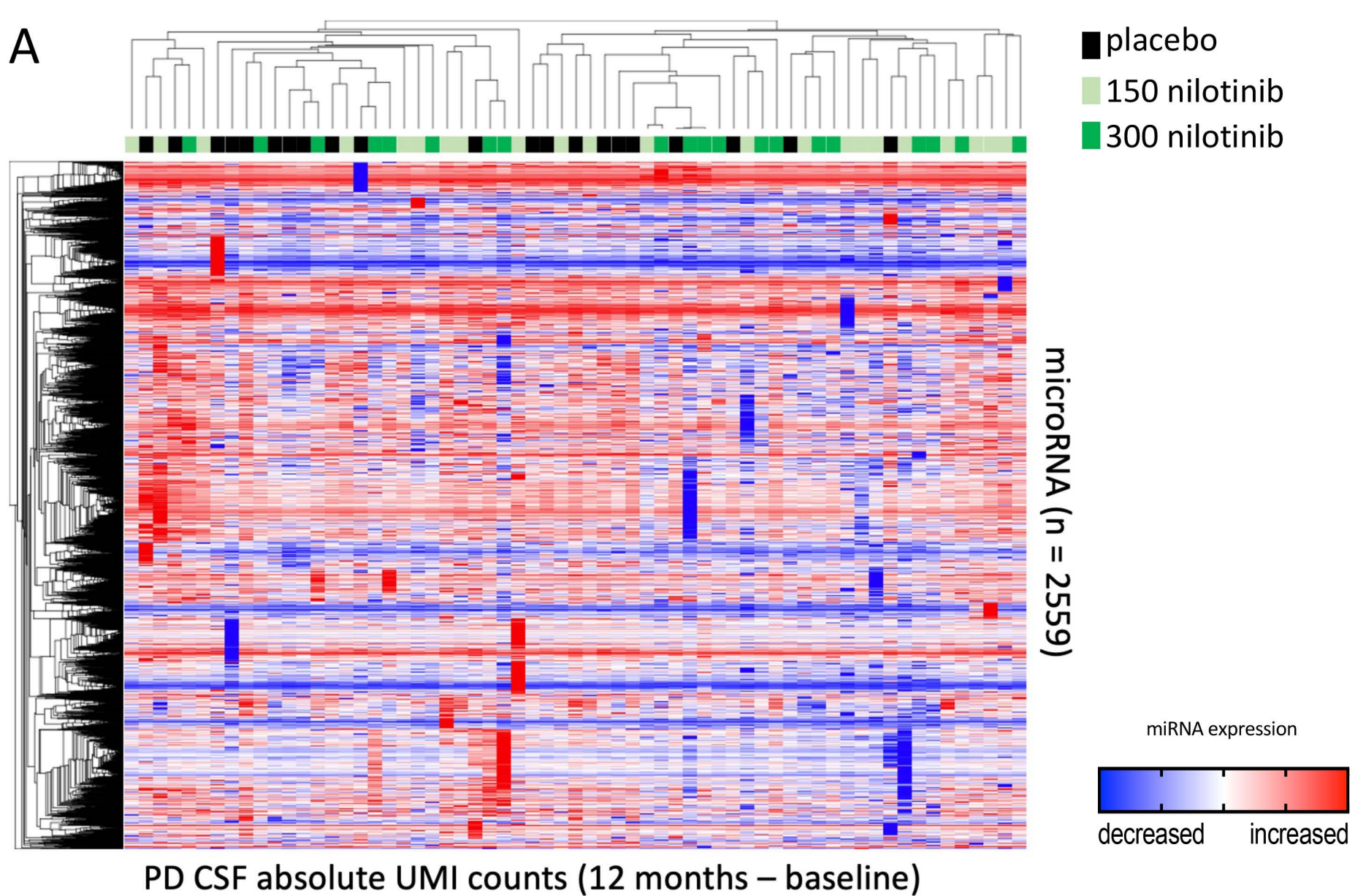
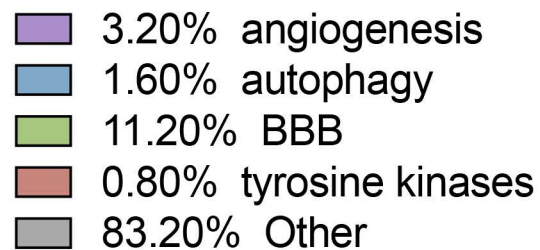
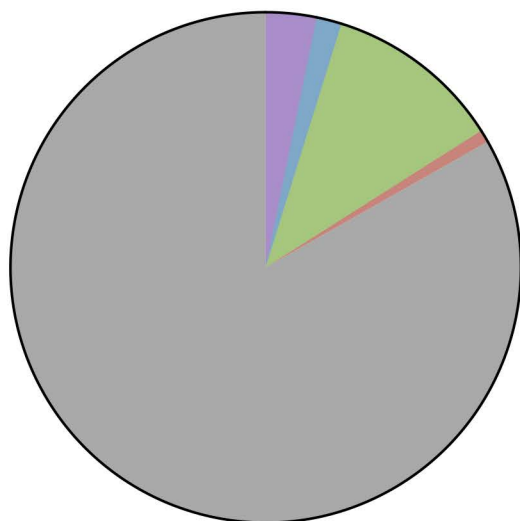




A

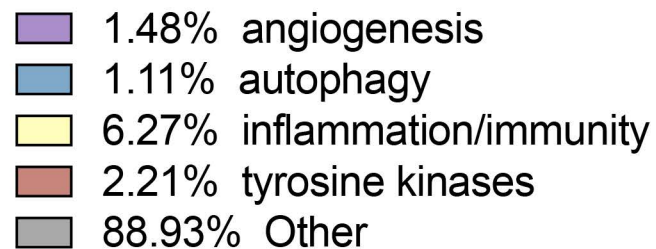
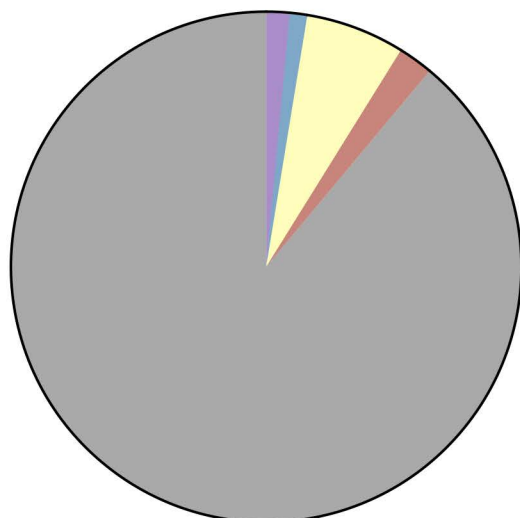
Placebo



125 pathways ($p_{\text{adj}} < 0.05$)

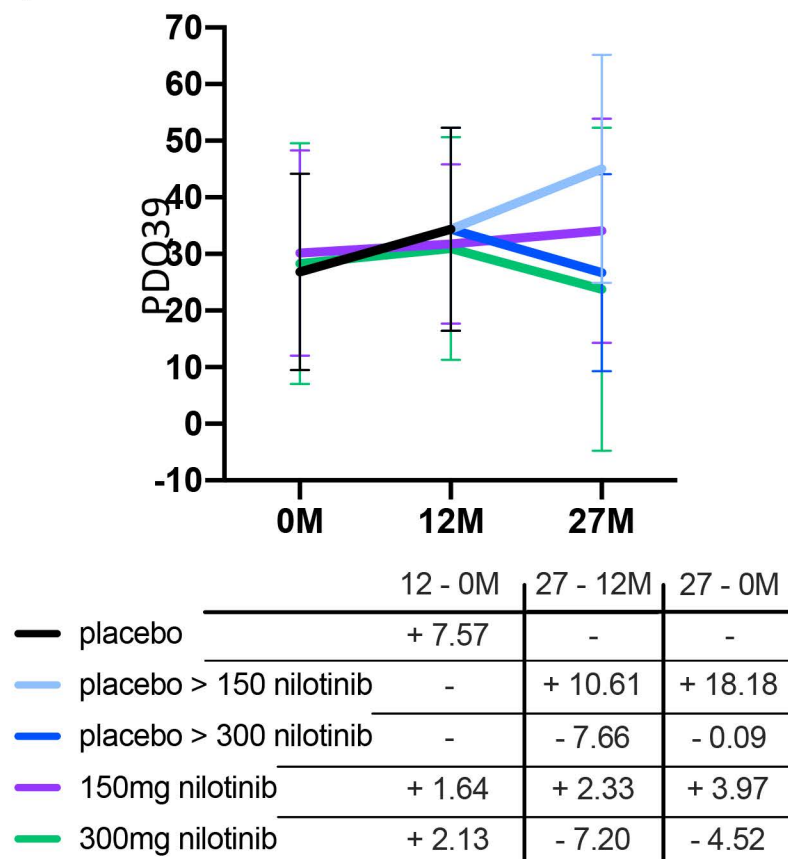
B

300mg nilotinib

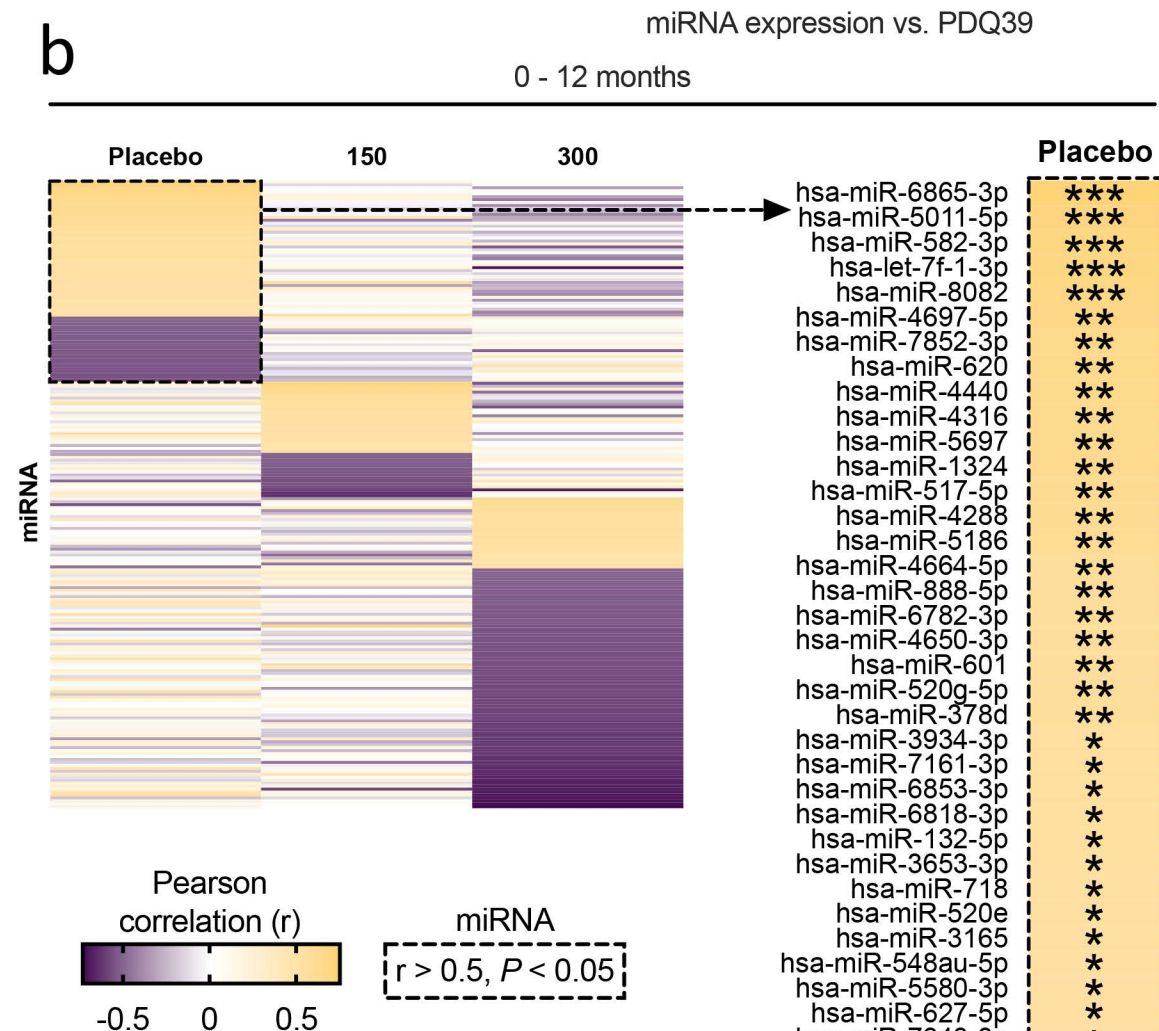


271 pathways ($p_{\text{adj}} < 0.05$)

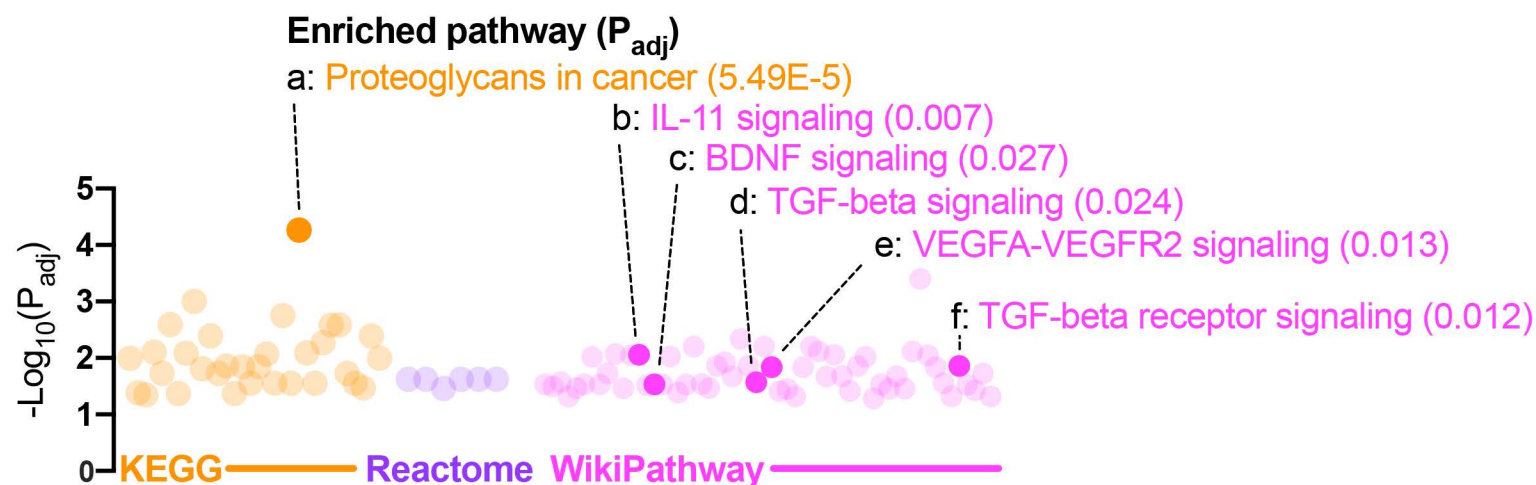
A



b



C



eFigure 1 Longitudinal microRNA expression. (A) Heatmap of the difference between 12 months and baseline absolute unique molecular identifiers (*UMIs*) for all 2559 miRNA mapped with hierarchical clustering performed using Morpheus (The Broad Institute). **(B)** Schematic of longitudinal miRNA expression analysis using Wald test and ME-ANOVA with Kruskal-Wallis test in parallel. This schematic was created using BioRender.com.

eFigure 2 Pathway and GO functional analysis demonstrate angiogenesis and BBB breakdown associated with placebo and inflammation and autophagy associated with 300mg nilotinib.

(A) Percentage of pathways associated with angiogenesis, autophagy, the BBB, and tyrosine kinases by placebo group DEMs. **(B)** Percentage of pathways associated with angiogenesis, autophagy, inflammation and immunity, and tyrosine kinases by 300mg nilotinib group DEMs.

eFigure 3 Correlating longitudinal miRNA expression to PDQ-39. (D) Parkinson's disease questionnaire (PDQ)-39 at 0, 12, and 27 months $\pm$ standard deviation. The difference in scores is shown below in the table. **(E)** Heatmap of the correlation between 12-months and longitudinal changes in PDQ-39 and longitudinal changes in miRNAs were computed using Spearman's rank correlations. Placebo group miRNAs that highly correlate to PDQ-39 ($r > 0.5$, $P < 0.05$) are outlined by dotted line and shown to the right. 27-months correlation when patients in placebo were transitioned to nilotinib, 150 or 300mg, for the second year (right). **(F)** KEGG, Reactome, and WikiPathway enrichment analysis of gene regulation by miRNA that highly correlate to PDQ-39 in placebo.

eTable 1. Cross-sectional miRNA expression during single-dose study

miRNA	Unique Molecular Identifiers (UMIs)						Fold-change from placebo			
	Placebo	150mg nilo	200mg nilo	300mg nilo	400mg nilo	Kruskal Wallis p-value	150mg nilo	200mg nilo	300mg nilo	400mg nilo
hsa-miR-100-5p	105.864	104.757	87.039	180.753	104.565	0.008	-0.010	-0.178	0.707	-0.012
hsa-miR-1233-5p	44.701	36.995	48.688	45.014	38.815	0.022	-0.172	0.089	0.007	-0.132
hsa-miR-124-3p	107.201	115.163	94.097	113.568	119.384	0.039	0.074	-0.122	0.059	0.114
hsa-miR-1260b	140.077	115.814	113.996	106.094	125.443	0.047	-0.173	-0.186	-0.243	-0.104
hsa-miR-1266-5p	160.906	202.500	182.801	187.439	160.894	0.010	0.258	0.136	0.165	0.000
hsa-miR-1268b	59.737	75.080	75.062	68.922	65.939	0.002	0.257	0.257	0.154	0.104
hsa-miR-1307-3p	132.348	131.699	119.363	147.233	118.421	0.026	-0.005	-0.098	0.112	-0.105
hsa-miR-1307-5p	126.377	111.316	129.411	111.968	129.015	0.029	-0.119	0.024	-0.114	0.021
hsa-miR-1321	72.323	76.776	67.093	62.788	63.846	0.026	0.062	-0.072	-0.132	-0.117
hsa-miR-133a-5p	87.009	77.223	90.696	89.021	81.207	0.036	-0.112	0.042	0.023	-0.067
hsa-miR-15a-3p	23.596	34.914	29.035	38.865	22.720	0.025	0.480	0.231	0.647	-0.037
hsa-miR-181a-2-3p	100.792	93.095	84.215	94.639	84.456	0.038	-0.076	-0.164	-0.061	-0.162
hsa-miR-190b	186.736	129.690	131.125	131.512	141.618	0.033	-0.305	-0.298	-0.296	-0.242
hsa-miR-194-5p	41.193	59.334	39.611	115.366	53.212	0.024	0.440	-0.038	1.801	0.292
hsa-miR-196a-3p	204.443	176.158	251.620	205.259	163.850	0.007	-0.138	0.231	0.004	-0.199
hsa-miR-196b-5p	44.385	45.257	54.024	58.935	45.750	0.029	0.020	0.217	0.328	0.031
hsa-miR-2117	78.267	76.849	70.617	75.543	71.484	0.050	-0.018	-0.098	-0.035	-0.087
hsa-miR-2277-5p	141.346	75.368	96.415	81.466	100.814	0.031	-0.467	-0.318	-0.424	-0.287
hsa-miR-26a-5p	337.376	351.951	308.023	942.082	339.861	0.041	0.043	-0.087	1.792	0.007
hsa-miR-323a-3p	50.598	44.173	36.706	41.298	49.753	0.015	-0.127	-0.275	-0.184	-0.017
hsa-miR-34a-3p	32.077	24.392	31.139	22.755	23.457	0.030	-0.240	-0.029	-0.291	-0.269
hsa-miR-3621	70.061	66.855	62.707	59.423	84.401	0.033	-0.046	-0.105	-0.152	0.205
hsa-miR-3668	103.739	106.860	106.485	103.236	98.497	0.036	0.030	0.026	-0.005	-0.051
hsa-miR-3678-3p	89.182	85.874	87.435	86.638	91.163	0.031	-0.037	-0.020	-0.029	0.022
hsa-miR-378f	54.944	60.948	65.244	47.029	45.912	0.017	0.109	0.187	-0.144	-0.164
hsa-miR-3936	63.603	80.846	78.296	77.358	73.563	0.048	0.271	0.231	0.216	0.157
hsa-miR-3972	129.954	117.571	125.785	120.997	143.315	0.001	-0.095	-0.032	-0.069	0.103
hsa-miR-4260	131.510	139.623	143.426	131.301	140.822	0.023	0.062	0.091	-0.002	0.071
hsa-miR-4265	19.239	29.653	27.634	27.916	33.438	0.036	0.541	0.436	0.451	0.738
hsa-miR-4427	47.855	43.930	43.371	51.047	53.214	0.011	-0.082	-0.094	0.067	0.112
hsa-miR-4429	128.152	105.572	115.517	111.604	134.158	0.041	-0.176	-0.099	-0.129	0.047
hsa-miR-4433b-3p	108.489	89.075	115.202	85.552	99.105	0.036	-0.179	0.062	-0.211	-0.087
hsa-miR-4515	79.019	70.698	73.336	71.041	67.641	0.012	-0.105	-0.072	-0.101	-0.144
hsa-miR-451a	110.280	136.579	131.143	5359.413	137.099	0.041	0.238	0.189	47.598	0.243
hsa-miR-4637	41.245	56.101	44.470	35.688	46.697	0.036	0.360	0.078	-0.135	0.132
hsa-miR-466	80.698	81.698	79.918	72.801	73.781	0.045	0.012	-0.010	-0.098	-0.086
hsa-miR-4663	72.354	64.004	61.027	56.618	136.479	0.014	-0.115	-0.157	-0.217	0.886
hsa-miR-4670-5p	55.245	49.752	57.462	48.338	56.181	0.042	-0.099	0.040	-0.125	0.017
hsa-miR-4686	618.387	663.635	634.069	555.733	597.121	0.042	0.073	0.025	-0.101	-0.034
hsa-miR-4736	67.739	64.449	53.192	62.492	80.880	0.038	-0.049	-0.215	-0.077	0.194
hsa-miR-4761-3p	29.040	19.887	23.021	21.688	30.604	0.013	-0.315	-0.207	-0.253	0.054
hsa-miR-4762-3p	74.569	73.798	74.769	63.752	76.728	0.023	-0.010	0.003	-0.145	0.029
hsa-miR-4764-3p	81.387	69.696	72.249	75.138	73.808	0.048	-0.144	-0.112	-0.077	-0.093
hsa-miR-4782-3p	37.719	43.846	41.749	35.950	40.642	0.031	0.162	0.107	-0.047	0.078
hsa-miR-4793-3p	142.040	164.303	167.987	154.162	163.154	0.022	0.157	0.183	0.085	0.149
hsa-miR-4795-3p	97.777	63.140	101.403	91.401	93.281	0.014	-0.354	0.037	-0.065	-0.046
hsa-miR-488-3p	101.231	86.896	96.825	86.186	115.164	0.045	-0.142	-0.044	-0.149	0.138
hsa-miR-490-5p	41.039	48.112	45.656	33.420	39.867	0.032	0.172	0.112	-0.186	-0.029
hsa-miR-5003-5p	77.839	64.140	82.482	75.992	80.003	0.000	-0.176	0.060	-0.024	0.028
hsa-miR-5095	110.085	113.042	98.097	102.873	125.396	0.044	0.027	-0.109	-0.066	0.139
hsa-miR-513b-5p	45.284	23.820	36.033	36.407	31.923	0.038	-0.474	-0.204	-0.196	-0.295
hsa-miR-5187-3p	64.555	72.061	72.139	81.584	70.159	0.012	0.116	0.117	0.264	0.087
hsa-miR-5195-3p	79.308	90.639	96.775	88.919	80.385	0.011	0.143	0.220	0.121	0.014
hsa-miR-522-3p	30.926	38.612	32.308	30.751	31.997	0.048	0.249	0.045	-0.006	0.035
hsa-miR-524-5p	54.245	40.621	46.788	57.646	47.150	0.012	-0.251	-0.137	0.063	-0.131
hsa-miR-545-5p	124.979	83.130	112.857	80.831	125.554	0.040	-0.335	-0.097	-0.353	0.005
hsa-miR-548ar-3p	26.049	11.913	19.465	16.897	22.152	0.031	-0.543	-0.253	-0.351	-0.150
hsa-miR-548v	61.565	72.002	69.804	64.106	64.459	0.017	0.170	0.134	0.041	0.047
hsa-miR-5572	126.140	118.211	141.398	133.399	122.263	0.025	-0.063	0.121	0.058	-0.031
hsa-miR-5702	115.590	112.754	124.189	112.350	124.049	0.034	-0.025	0.074	-0.028	0.073
hsa-miR-5707	94.163	104.670	102.731	90.914	103.423	0.031	0.112	0.091	-0.035	0.098
hsa-miR-592	276.254	231.283	266.022	276.290	253.109	0.045	-0.163	-0.037	0.000	-0.084
hsa-miR-605-3p	66.895	52.202	46.652	55.326	62.432	0.003	-0.220	-0.303	-0.173	-0.067
hsa-miR-6127	32.355	39.434	43.325	37.234	34.823	0.036	0.219	0.339	0.151	0.076
hsa-miR-620	31.859	28.461	25.908	24.087	23.973	0.014	-0.107	-0.187	-0.244	-0.248
hsa-miR-644a	137.924	96.751	158.556	137.255	100.764	0.044	-0.299	0.150	-0.005	-0.269
hsa-miR-645	59.094	34.508	42.243	39.621	59.068	0.014	-0.416	-0.285	-0.330	0.000
hsa-miR-6500-3p	50.792	59.431	67.670	53.864	56.679	0.007	0.170	0.332	0.060	0.116
hsa-miR-6512-5p	33.355	41.381	29.144	34.887	30.514	0.045	0.241	-0.126	0.046	-0.085
hsa-miR-660-5p	56.869	69.222	62.599	107.722	65.168	0.033	0.217	0.101	0.894	0.146
hsa-miR-6781-3p	54.975	61.949	63.432	56.912	61.924	0.035	0.127	0.154	0.035	0.126

hsa-miR-6785-3p	87.022	94.342	86.267	93.404	109.299	0.034	0.084	-0.009	0.073	0.256
hsa-miR-6790-5p	201.715	160.695	154.183	139.909	156.223	0.012	-0.203	-0.236	-0.306	-0.226
hsa-miR-6797-3p	43.221	52.059	54.989	56.931	52.343	0.047	0.205	0.272	0.317	0.211
hsa-miR-6809-3p	61.251	64.602	67.155	68.773	79.846	0.006	0.055	0.096	0.123	0.304
hsa-miR-6815-5p	131.296	144.528	114.773	106.985	112.539	0.031	0.101	-0.126	-0.185	-0.143
hsa-miR-6817-5p	49.687	80.040	60.723	63.689	50.922	0.015	0.611	0.222	0.282	0.025
hsa-miR-6836-3p	44.296	35.414	34.540	31.663	45.471	0.014	-0.201	-0.220	-0.285	0.027
hsa-miR-6836-5p	34.307	33.017	43.440	31.320	51.009	0.022	-0.038	0.266	-0.087	0.487
hsa-miR-6838-5p	101.845	67.853	67.351	71.726	94.736	0.049	-0.334	-0.339	-0.296	-0.070
hsa-miR-6840-3p	48.627	38.488	55.316	46.964	39.864	0.047	-0.209	0.138	-0.034	-0.180
hsa-miR-6842-5p	52.247	58.013	60.188	56.146	64.205	0.046	0.110	0.152	0.075	0.229
hsa-miR-6843-3p	45.994	50.145	54.964	41.003	43.108	0.030	0.090	0.195	-0.108	-0.063
hsa-miR-6848-5p	35.999	48.779	52.691	43.067	44.862	0.035	0.355	0.464	0.196	0.246
hsa-miR-6861-5p	90.895	101.775	107.552	95.726	115.851	0.012	0.120	0.183	0.053	0.275
hsa-miR-6884-5p	166.765	197.894	195.271	183.786	174.248	0.006	0.187	0.171	0.102	0.045
hsa-miR-6885-3p	46.007	33.154	38.238	41.267	34.942	0.027	-0.279	-0.169	-0.103	-0.241
hsa-miR-7978	45.099	47.109	35.003	33.402	44.433	0.014	0.045	-0.224	-0.259	-0.015
hsa-miR-889-5p	349.162	358.303	409.740	419.573	411.747	0.023	0.026	0.173	0.202	0.179
hsa-miR-920	44.737	38.723	48.211	38.620	40.358	0.039	-0.134	0.078	-0.137	-0.098
hsa-miR-924	77.631	72.933	82.054	77.464	82.730	0.001	-0.061	0.057	-0.002	0.066
hsa-miR-934	68.855	59.715	62.900	58.800	56.119	0.038	-0.133	-0.086	-0.146	-0.185
hsa-miR-95-5p	80.155	89.002	89.352	81.641	80.051	0.031	0.110	0.115	0.019	-0.001

Table 2. Longitudinal changes in UPDRS II + III

Treatment	UPDRS II+III longitudinal changes					
	0M	12M	27M	Δ 12-0M	Δ 27-12M	Δ 27-0M
placebo	40.9 $\pm$ 7.2	43.3 $\pm$ 12.2		2.39		
placebo > 150 nilo			51.1 $\pm$ 15		7.8	10.19
placebo > 300 nilo			37.6 $\pm$ 9		-5.7	-3.31
150 nilotinib	41.7 $\pm$ 9.2	41.6 $\pm$ 11	42.2 $\pm$ 15.7	-0.14	0.57	0.43
300 nilotinib	43.7 $\pm$ 8.3	43.7 $\pm$ 11	40.2 $\pm$ 11.1	-0.05	-3.41	-3.46