Preclinical Efficacy of a Carboxylesterase 2-Activated Prodrug of Doxazolidine, Pentyl PABC-Doxaz

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Supporting Information

Statistical Analysis of Inhibition of H1435 Tumor Growth
Cell Growth Data – Doxaz
Cell Growth Data – Pentyl PABC-Doxaz
Statistical Analysis of Cell Data

Table of mean difference in growth of H1435 tumors and p value for each treatment comparison at different time intervals.

	Day 14 to 77			Day 14 to 28			Day 14 to 35		
	Mean Difference	**Standard** Error	**P-value**	**Mean** Difference	**Standard** Error	**P-value**	**Mean** Difference	**Standard** Error	**P-value**
PPD4 vs. PPD3	-0.32	0.47	0.4937	-1.10	0.32	0.0017*	-0.91	0.33	0.0097*
PPD4 vs. Dox	-0.68	0.44	0.1307	-1.59	0.30	<.0001*	-1.30	0.31	0.0002*
PPD4 vs. Control	-1.99	0.44	<.0001*	-1.51	0.30	<.0001*	-1.57	0.31	<.0001*
PPD3 vs. Dox	-0.35	0.45	0.4367	-0.49	0.31	0.1188	-0.39	0.32	0.2231
PPD3 vs. Control	-1.67	0.44	0.0006*	-0.41	0.31	0.1899	-0.66	0.31	0.0432
Dox vs. Control	-1.31	0.43	0.0045*	0.09	0.30	0.7766	-0.27	0.31	0.3932

	Day 35 to 56			Day 63 to 77			Day 63 to 77 vs. Day 14 to 28		
	Mean Difference	**Standard** Error	**P-value**	**Mean** Difference	**Standard** Error	**P-value**	**Mean** Difference	**Standard** Error	**P-value**
PPD4 vs. PPD3	-0.49	0.52	0.3540	0.68	0.65	0.3008	1.78	0.50	0.0012*
PPD4 vs. Dox	-0.56	0.49	0.2582	0.09	0.60	0.8804	1.69	0.47	0.0010*
PPD4 vs. Control	-2.08	0.49	0.0002*	-2.35	0.61	0.0004*	-0.84	0.47	0.0831
PPD3 vs. Dox	-0.07	0.50	0.8897	-0.59	0.62	0.3491	-0.09	0.48	0.8503
PPD3 vs. Control	-1.58	0.50	0.0030*	-3.03	0.61	<.0001*	-2.62	0.48	<.0001*
Dox vs. Control	-1.51	0.49	0.0036*	-2.45	0.60	0.0002*	-2.53	0.47	<.0001*

* Significant difference with Bonferroni-Holm correction (i.e., 0.05/6=0.0083 for smallest p-value, 0.05/5=0.01 for second smallest p-value, 0.05/4=0.0125 for third smallest p-value, etc, sequentially).
**Adjusted mean, after adjusting day 7 as covariate throughout the model. The difference is computed as the first treatment minus the second treatment in the pairwise comparison.

Table of Cell Growth Data for NCI Treatments with Doxaz

| | Trial 1 | | | | | | Trial 2 | | | | | |
| | Concentrations (log M) | | | | | | Concentrations (log M) | | | | | |
Cell Line	Veh	-10	-9	-8	-7	-6	Veh	-10	-9	-8	-7	-6
CCRF-CEM	1.13	0.91	0.7	0.44	0.25	0.2	0.8	0.54	0.48	0.27	0.17	0.15
HL-60(TB)	1.1	0.94	0.61	0.34	0.21	0.18	1.19	0.78	0.62	0.3	0.21	0.2
K-562	1.4	1.36	1.19	0.74	0.22	0.18	1.12	0.91	0.8	0.39	0.14	0.12
MOLT-4	1.08	0.83	0.58	0.3	0.24	0.18	1.39	0.93	0.76	0.41	0.3	0.27
RPMI-8226	0.46	0.42	0.36	0.2	0.15	0.11	1	0.88	0.82	0.38	0.21	0.21
SR	0.4	0.4	0.26	0.14	0.12	0.08	0.61	0.43	0.36	0.19	0.15	0.13
A549-ATCC	1.55	1.43	1.31	1.02	0.42	0.4	0.76	0.67	0.62	0.37	0.19	0.2
EKVX	1.84	1.86	1.8	1.84	1	0.76	1.31	1.26	1.31	1.27	0.45	0.5
HOP-62	1.53	1.42	1.29	0.92	0.62	0.44	1.11	1.15	1.08	0.77	0.44	0.31
HOP-92	1.03	0.99	0.93	0.8	0.58	0.47	1.01	0.88	0.85	0.65	0.47	0.43
NCI-H226	0.99	0.97	0.98	0.75	0.39	0.25	2.05	1.84	1.76	1.47	0.8	0.59
NCI-H23	1.61	1.55	1.37	0.96	0.34	0.25	1.37	1.28	1.17	0.71	0.2	0.19
NCI-H322M	1.31	1.34	1.28	1.23	0.62	0.49	0.96	0.95	1.01	0.93	0.53	0.52
NCI-H460	0.67	0.5	0.3	0.19	0.09	0.05	1.42	0.71	0.55	0.29	0.19	0.12
NCI-H522	1.79	1.67	1.63	1.38	0.5	0.36	0.87	0.81	0.84	0.51	0.26	0.27
COLO-205	0.71	0.68	0.7	0.51	0.07	0.04	0.55	0.44	0.5	0.36	0.04	0.06
HCC-2998	1.28	1.29	1.26	1.06	0.35	0.11	0.94	0.8	0.77	0.67	0.17	0.04
HCT-116	1.38	1.3	1.14	0.82	0.26	0.21	0.99	0.88	0.75	0.32	0.15	0.12
HCT-I5	2.47	2.13	2.24	1.97	0.96	0.51	0.66	0.68	0.6	0.49	0.11	0.09
HT29	0.42	0.42	0.32	0.23	0.07	0.05						
KM12	1.12	1.07	0.98	0.86	0.31	0.25	0.99	0.89	0.98	0.74	0.34	0.34
SW-620	1.45	1.33	1.14	0.82	0.37	0.31	1.11	0.87	0.83	0.51	0.21	0.22
SF-268	0.52	0.52	0.44	0.3	0.17	0.15	0.98	0.8	0.7	0.41	0.27	0.24
SF-295	0.88	0.85	0.74	0.54	0.31	0.26	0.85	0.78	0.83	0.47	0.37	0.4
SF-539	1.93	1.96	1.93	1.26	0.52	0.36	2.37	2.25	2.4	1.74	0.75	0.61
SNB-19	0.83	0.54	0.76	0.52	0.29	0.24	1.32	1.12	1.15	0.76	0.43	0.5
SNB-75	0.98	0.98	0.95	0.82	0.21	0.12	1.06	0.99	1.01	0.78	0.14	0.11
U251	1.35	1.25	1.04	0.71	0.32	0.25	0.42	0.35	0.31	0.14	0.09	0.08
LOX-IMVI	1.96	1.65	1.48	0.9	0.43	0.3	0.89	0.68	0.57	0.18	0.12	0.08
MALME-3M	0.95	1.03	0.98	0.9	0.31	0.25	0.86	0.82	0.89	0.78	0.38	0.43
M14	1.36	1.33	1.19	0.85	0.34	0.06	1.26	1.2	1.12	0.69	0.19	0.05
MDA-MB-435	1.16	1.14	1	0.86	0.25	0.09	1.48	1.52	1.53	1.16	0.31	0.24
SK-MEL-2	1.98	2.06	2.07	1.96	0.43	0.33	1.29	1.27	1.38	0.9	0.29	0.31
SK-MEL-28	1.09	1.11	1.07	1.01	0.26	0.14	1.98	1.96	2.02	1.72	0.47	0.26
SK-MEL-5	2.13	2.1	1.93	1.47	0.37	0.29	2.78	2.72	2.83	2.19	0.44	0.21
UACC-257	1.37	1.36	1.38	1.3	0.52	0.47	0.74	0.66	0.67	0.55	0.19	0.21
UACC-62							1.72	1.6	1.51	0.87	0.12	0.11
IGROVI	1.66	1.48	1.38	1	0.33	0.66	0.86	0.6	0.57	0.43	0.28	0.31
OVCAR-3	0.83	0.86	0.83	0.66	0.29	0.29	1.21	1.29	1.22	1.02	0.52	0.56
OVCAR-4	0.81	0.84	0.83	0.78	0.43	0.36						
OVCAR-5	0.83	0.85	0.83	0.76	0.38	0.36	0.8	0.83	0.82	0.79	0.42	0.45
OVCAR-8	1.13	1.05	0.99	0.79	0.35	0.3	0.64	0.52	0.55	0.35	0.22	0.18
NCI/ADR-RES	1.75	1.69	1.64	1.46	0.69	0.54	1.52	1.46	1.43	1.15	0.52	0.41
SK-OV-3	0.9	1.07	0.91	0.83	0.48	0.47	1.05	1.03	1.09	0.79	0.61	0.57
786-0							2.41	2.35	2.19	0.85	0.78	0.67
A498	1.59	1.51	1.49	1.35	0.71	0.54	1.76	1.71	1.75	1.61	0.68	0.5
ACHN	1.22	1.1	0.89	0.52	0.3	0.23	0.56	0.47	0.41	0.2	0.12	0.12
CAKI-1	1.14	1.07	0.86	0.45	0.33	0.29	1.47	1.22	1.18	0.84	0.45	0.5
RXF	0.32	0.91	0.86	0.8	0.61	0.15	0.73	0.63	0.63	0.43	0.21	0.2
SN12C	0.84	0.87	0.83	0.61	0.41	0.28	1.9	1.73	1.64	1.35	0.73	0.63
TK-IO	1.3	1.33	1.24	1.18	0.58	0.53	1.1	1.04	1.14	0.99	0.61	0.63
UO-31	1	0.9	0.82	0.6	0.27	0.27	1.13	1.07	1.06	0.84	0.43	0.52
PC-3							1.39	1.33	1.25	0.88	0.34	0.2
DU-145	0.86	0.83	0.68	0.33	0.26	0.23	1.24	1.11	1.1	0.49	0.38	0.42
MCF-7	0.69	0.64	0.54	0.36	0.22	0.17	0.65	0.55	0.49	0.27	0.19	0.13
MDA-MB-23I/ATCC	0.48	0.49	0.46	0.4	0.24	0.14	0.66	0.64	0.64	0.55	0.27	0.21
HS5787T	1.22	1.27	1.21	1.16	0.73	0.63	1.16	1.15	1.19	1.03	0.62	0.58
BT-549	1.91	1.92	1.83	1.64	0.79	0.61	1.29	1.2	1.27	1	0.06	0.6
T-47D	1	1.08	0.92	0.66	0.41	0.38	0.9	0.74	0.74	0.53	0.37	0.39

Table of Cell Growth Data for NCI Treatments with pentyl PABC-Doxaz

	Trial 1 Concentrations (log M)						Trial 2 Concentrations (log M)					
Cell Line	Veh	-10	-9	-8	-7	-6	Veh	-10	-9	-8	-7	-6
CCRF-CEM	1.49	1.53	1.5	1.36	1.07	0.3	1.17	1.5	1.09	0.63	0.66	0.81
HL-60(TB)	1.95	2.03	2	1.5	1.1	0.4	0.8	0.8	0.65	0.44	0.39	0.09
K-562	0.5	0.51	0.5	0.44	0.31	-0	1.05	0.8	0.81	0.67	0.45	0.08
MOLT-4	1.66	1.49	1.4	1.4	0.84	0.3	1.01	0.9	0.73	0.53	0.27	0.12
RPMI-8226	2.23	2.29	2.1	1.83	1.64	0.5	1.78	1.8	1.5	1.33	1.39	0.63
SR	1.32	1.32	1.2	0.9	0.6	0.2	0.83	0.8	0.64	0.36	0.21	0.05
A549/ATCC	1.96	1.89	1.6	1.3	1.12	0.5	1.55	1.4	1.12	0.97	0.76	0.27
EKVX	1.12	1.02	1	0.94	0.97	0.3	1.49	1.5	1.43	1.39	1.26	0.67
HOP-62	1.41	1.38	1.3	1.18	0.93	0.3	1.26	1.2	1.16	1.06	0.75	-0.1
HOP-92	1.31	1.32	1.2	1.18	0.99	0.6	0.93	1	0.87	0.79	0.71	0.3
NCI-H226	1.53	1.58	1.5	1.35	1.22	-0	1.93	1.9	1.66	1.42	1.34	0.36
NCI-H23	0.75	0.67	0.7	0.7	0.75	0.5	1.62	1.6	1.53	1.34	1.11	0.2
NCI-H322M	1.19	1.29	1.1	1.03	0.97	0.5	1.34	1.3	1.19	1.24	1.11	0.85
NCI-H460	1.96	1.92	1.8	0.99	0.64	-0	2.39	2.2	1.6	0.95	0.71	0.33
NCI-H522	1.89	1.83	1.7	1.7	1.59	0.6	0.76	0.7	0.7	0.67	0.57	0.32
COLO 205	1.02	1.03	0.9	0.87	0.74	0.1	1.34	1.3	1.27	1.16	1.1	0.72
HCC-2998	1.46	1.42	1.4	1.21	1.17	0.4	2.04	1.9	1.93	1.33	1.6	0.63
HCT-116	1.27	1.21	1.1	1.05	0.83	-0	1.08	1	1.15	0.87	0.58	0.1
HCT-15	1.63	1.56	1.6	1.45	1.28	0.2	1.4	1.4	1.36	1.2	1.04	0.3
HT29	0.69	0.63	0.6	0.59	0.43	-0	1.14	1.1	0.99	0.88	0.71	0.32
KM12	1.72	1.65	1.8	1.54	1.5	1.1	1.09	1.1	1.05	1.03	0.91	0.33
SW-620	0.56	0.55	0.5	0.48	0.33	-0	1.13	1	0.98	0.87	0.6	0.37
SF-268	1.22	1.2	1.1	0.94	0.87	0.4	1.15	1.1	1.06	0.87	0.7	0.34
SF-295	2.35	2.23	2.1	1.71	1.45	0.7	1.82	1.9	1.63	1.14	1	0.51
SF-539	1.42	1.2	1.2	1.13	0.95	0.1	1.83	1.8	1.87	1.71	1.19	0.48
SNB-19	1.25	1.24	1.2	1.02	0.84	0.5	1.66	1.6	1.58	1.47	1.34	0.88
SNB-75	0.96	0.94	0.9	0.91	0.82	0.3	1.28	1.2	1.21	1.04	0.98	0.54
U251	1.53	1.53	1.5	1.32	1.09	0.3	1.27	1.3	1.2	1.09	0.71	0.02
LOX IMVI	2.13	2.1	1.9	1.75	1.49	-0	1.62	1.5	1.37	1.28	0.8	0.08
MALME-3M	0.83	0.85	0.8	0.82	0.8	0.7	1.04	1.1	1.06	1.09	0.99	0.36
M14							1.24	1.2	1.04	0.89	0.71	0.06
MDA-MB-435	1.38	1.33	1.2	1.15	1.11	0.2	1.38	1.4	1.15	1.14	1.01	0.54
SK-MEL-2	2.23	2.21	2.2	2.25	2.19	1.2	1.93	1.9	1.99	1.92	2.08	1.03
SK-MEL-28	0.75	0.72	0.8	0.75	0.65	0.3	1.2	1.2	1.22	1.11	1.11	0.7
SK-MEL-5	1.71	1.58	1.3	0.96	0.8	-0	1.26	1	0.75	0.63	0.43	0.12
UACC-257	1.78	1.88	1.6	1.42	1.47	0.8	1.83	1.8	1.5	1.41	1.33	0.73
UACC-62	1.94	1.98	1.9	1.79	1.62	0.3	2.39	2.4	2.25	1.87	1.58	0.17
IGROV1	1.47	1.39	1.3	1.12	1.04	0.3	1.8	1.6	1.61	1.37	1.21	0.15
OVCAR-3	1.17	1.1	1	1.09	1.04	0.3	0.97	1	0.97	0.9	0.8	-0
OVCAR-4	1	0.96	0.9	0.81	0.78	0.3	1.4	1.3	1.21	1.17	1.06	0.77
OVCAR-5	1.19	1.14	1.1	0.94	0.82	0.2	2.13	1.9	1.83	1.8	1.79	0.82
OVCAR-8	1.63	1.64	1.5	1.29	1.06	0.5	1.89	1.9	1.66	1.4	1.23	0.54
NCI/ADR-RES	1.62	1.62	1.6	1.37	1.24	0.6	1.1	1.1	0.98	0.89	0.78	0.62
SK-OV-3	1.12	1.12	1	0.64	0.57	0.5	1.09	1.1	0.81	0.58	0.67	0.46
786-0	0.96	0.73	0.8	0.56	0.56	0.2	2.19	2.2	1.98	1.42	1.16	-0
A498	1.28	1.22	1.1	0.52	0.14	-0						
ACHN	1.51	1.45	1	0.57	0.51	0	1.29	1.1	0.54	0.46	0.47	0.23
CAKI-1	1.87	1.73	1.6	1.2	0.81	-0	0.8	0.8	0.7	0.53	0.44	0
RXF393	1.25	1.23	1.2	1.08	1.05	0.4	1.25	1.2	1.23	1.06	1.02	0.14
SN12C	1.73	1.74	1.6	1.14	1.08	0.6	1.77	1.8	1.6	1.18	1.1	0.72
TK-10							1.11	1.1	1.06	0.99	0.98	0.31
UO-31	1.36	1.36	1.1	0.84	0.79	0.4	2.17	2.1	1.72	1.26	1.16	0.45
PC-3	1.37	1.41	1.3	1.16	1.12	0.4	0.93	0.9	0.91	0.84	0.73	0.25
DU-145	0.75	0.57	0.5	0.45	0.35	-0	1.12	1.2	0.94	0.82	0.52	0.06
MCF7	0.98	0.96	0.9	0.67	0.59	0.1	2.04	2	1.71	1.09	0.89	0.54
MDA-MB-231/ATCC	1.04	1.02	1	0.96	0.88	0.3	1.34	1.4	1.33	1.19	1.09	0.4
HS 578T	1.16	1.12	1.1	1.02	0.94	0.6	0.83	0.8	0.76	0.77	0.68	0.43
BT-549	0.96	0.64	0.6	0.56	0.48	-0	1.29	1.3	1.27	1.09	1.01	0.5
T47D	1.58	1.53	1.5	1.28	1.03	0.8	1.33	1.3	1.29	1.09	0.96	0.76

Statistical Analysis for NCI Cell Growth Data

Full Model: $\log PPD\ IC_{50} = C_1(\log Doxaz\ IC_{50}) - C_2(\log CES2) + C_3$

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	19.17968603	9.58984301	32.38	<.0001
Error	56	16.58277998	0.29612107		
Corrected Total	58	35.76246601			

Correlation

R^2	Coeff Var	Root MSE	logPPD Mean
0.536308	-11.49055	0.544170	-4.735805

Coefficients

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	6.587000693	1.42630883	4.62	<.0001
logCES2	-3.200853137	0.53112232	-6.03	<.0001
logDoxaz	0.520158073	0.09787031	5.31	<.0001