

Supplemental Information: On-line only Appendix

The First-in-human Phase 1 Dose Escalation Study of the SMAC-Mimetic Birinapant in Adults with Refractory Solid Tumors or Lymphoma

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Supplemental Table S1. Patient Disposition

Status	All Patients n (%)
Safety Population	50 (100)
Evaluable for Cycle 1 DLT Assessment	48 (96)
Efficacy Population	26 (52)
Primary Reason for Discontinuation	
Lack of Efficacy	38 (76)
Adverse Event	6 (12)
Physician Decision	3 (6)
Voluntarily Withdrew	2 (4)
Patient Died	1 (2)

Supplemental Table S2. M30 and M65 Fragments of Cytokeratin-18 (CK-18) for the cohort with the greatest number of patients (47 mg/m²; n=17^a) and for all patients (n=50)

	<u>C1D1</u>			<u>C1D8</u>		<u>C1D15</u>		
	Baseline	4hr	24 hr	pre-dose	4hr	pre-dose	4hr	24hr
47mg/m² (n=17)								
M30	174	193	173	239	243	307	269	270
U/L	(90-1583)	(102-1437)	(99-1758)	(106-1283)	(86-1400)	(104-1380)	(88-1377)	(86-2004)
M65	522	706	587	699	620	776	807	719
U/L	(190-7515)	(220-6367)	(222-6389)	(248-5724)	(209-5786)	(337-6507)	(261-6052)	(308-8591)
All patients (n=50)								
M30	142	147	156	167	138	182	163	174
U/L	(78-1583)	(81-1437)	(83-1758)	(81-1283)	(79-1400)	(81-1937)	(82-1696)	(68-2004)
M65	506	566	587	589	585	703	645	650
U/L	(172-7515)	(188-6367)	(179-6389)	(179-5724)	(181-5786)	(174-6507)	(195-6052)	(152-8591)

Results are median (range) U/L

^a Results are shown for patients in both the dose-escalation phase (cohort 11) and expansion phase

Supplemental Table 3. Levels of M65 in Cohorts 1, 2, 3.

<u>C1D1</u>		<u>C1D8</u>	<u>C1D15</u>	
<u>Baseline</u>	<u>24hr</u>	<u>pre-dose</u>	<u>pre-dose</u>	<u>24hr</u>
Cohort 1 (0.18 mg/m²)				
965	1039	N/A	1358	2794
(465-3293)	(409-3691)	N/A	(494-4008)	(1289-4298)
Cohort 2 (0.36 mg/m²)				
570	740	591	717	801
(357-2248)	(475-2383)	(390-792)	(296-2054)	(438-2227)
Cohort 3 (0.72 mg/m²)				
374	436	352	468	575
(365-633)	(417-715)	(319-607)	(342-637)	(474-637)

Results are median (range) of M65 (U/L) for the lowest 3 dose cohorts

N/A= Not available

Supplemental Table 4. Levels of Caspase 3/7 for the cohort with the greatest number of patients (47 mg/m²; n=17^a) and for all patients (n=50)

	<u>C1D1</u>			<u>C1D8</u>		<u>C1D15</u>		
47mg/m² (n=17)								
	Baseline	4hr	24 hr	pre-dose	4hr	pre-dose	4hr	24hr
	158	183	180	164	196	183	199	207
	(110-231)	(118-261)	(103-269)	(126-317)	(127-331)	(118-453)	(126-346)	(129-306)
All patients (n=50)								
	173	198	191	187	209	199	209	209
	(92-508)	(118-554)	(89-583)	(109-317)	(127-342)	(111-560)	(126-507)	(115-371)

Results are median (range) RLU

^a Results are shown for patients in both the dose-escalation phase (cohort 11) and expansion phase

Supplemental Table 5. Analytes examined by Myriad RBM

Alpha-1 Antitrypsin	Fatty Acid Binding Protein, heart
Adiponectin	Factor VII
Alpha-2 Macroglobulin	Ferritin
Alpha-Fetoprotein	FGF basic
Apolipoprotein A1	Fibrinogen
Apolipoprotein CIII	Granulocyte-CSF
Apolipoprotein H	Growth Hormone
Beta-2 Microglobulin	Granulocyte-Macrophage-CSF
Brain-Derived Neurotrophic Factor	Haptoglobin
Complement C3	ICAM-1
Cancer Antigen 125	IFN-gamma
Cancer Antigen 19-9	IgA
Calcitonin	IgE
CD40 antigen	IGF-1
CD40 Ligand	IgM
Carcinoembryonic Antigen	IL-10
Creatine Kinase-MB	IL-12p40
C Reactive Protein	IL-12p70
Epidermal Growth Factor	IL-13
ENA-78	IL-15
Endothelin-1	IL-16
EN-RAGE	IL-18
Eotaxin - 1	IL-1alpha
Erythropoietin	IL-1beta

IL-1ra	Plasminogen Activator Inhibitor-1
IL-2	Prostatic Acid Phosphatase
IL-3	Prostate-Specific Antigen, Free
IL-4	T-Cell-Specific Protein RANTES
IL-5	Serum Amyloid P-Component
IL-6	Stem Cell Factor
IL-7	Serum Glutamic Oxaloacetic Transaminase
IL-8	Sex Hormone-Binding Globulin
Insulin	Thyroxine-Binding Globulin
Leptin	Tissue Factor
Apolipoprotein a	Tissue Inhibitor of Metalloproteinases 1
Lymphotoctin	Tumor Necrosis Factor alpha
Monocyte Chemo-attractant Protein 1	Tumor Necrosis Factor beta
Macrophage Derived Chemokine	Tumor Necrosis Factor Receptor-Like 2
Macrophage Inhibitory Protein-1alpha	Thrombopoietin
Macrophage Inhibitory Protein-1beta	Thyroid-Stimulating Hormone
Matrix Metalloproteinase-2	Vascular Cell Adhesion Molecule-1
Matrix Metalloproteinase-3	Vascular Endothelial Growth Factor
Matrix Metalloproteinase-9	von Willebrand Factor
Myeloperoxidase	
Myoglobin	