Supporting Information

The Discovery of a Potent Small-Molecule Antagonist of cIAP1/2 and XIAP Proteins and Clinical Candidate for the Treatment of Cancer (GDC-0152)

John A. Flygare,[*,†] Maureen Beresini,[‡] Nageshwar Budha,[#] Helen Chan,[ǁ] Iris T. Chan,[⊥] Sravanthi Cheeti,[#] Frederick Cohen,[†] Kurt Deshayes,[§] Karl Doerner,[¶] S. Gail Eckhardt,[⇑] Linda O. Elliott,[‡] Bainian Feng,[†] Matthew C. Franklin,[§] Stacy Frankovitz Reisner,[‡] Lewis Gazzard,[†] Jason Halladay,[ǁ] Sarah G. Hymowitz,[◊] Hank La,[ǁ] Patricia LoRusso,[⇓] Brigitte Maurer,[◊] Lesley Murray,[¶] Emile Plise,[ǁ] Clifford Quan,[§] Jean-Philippe Stephan,[‡] Young G. Shin,[ǁ] Jeffrey Tom,[§] Vickie Tsui,[†] Joanne Um,[†] Eugene Varfolomeev,[§] Domagoj Vucic,[§] Andrew J. Wagner,[∞] Heidi J.A. Wallweber,[◊] Lan Wang,[†] Joseph Ware,[#] Zhaoyang Wen,[†] Harvey Wong,[ǁ] Jonathan M. Wong,[†] Melisa Wong,[†] Susan Wong,[ǁ] Ron Yu,[▽] Kerry Zobel,[§] and Wayne J. Fairbrother*[,§]*

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Table S1. X-ray data collection and refinement statistics

Protein Construct	ML-IAP/XIAP chimera (MLXBIR3SG)	cIAP1/XIAP chimera (cXBIR3CS)
Resolution (Å)	50 – 1.71 (1.75 – 1.71)	31.36 – 1.79 (1.83 – 1.79)
Space Group	$P4_12_12$	$P2_12_12_1$
Unit cell (Å)	a = 87.4, c = 73.5	a = 35.7, b = 37.4, c = 57.6
Unique reflections	29,746 (2,145)	6,767 (369)
R_{sym} [b]	0.055 (0.346)	0.085 (0.467)
$\langle I/\sigma(I)\rangle$	32.9 (5.7)	13 (2.5)
Redundancy	7.9 (8.0)	3.3 (3.3)
R_{cryst} [c]	0.154	0.177
R_{free} [d]	0.162	0.230
Bond RMSD (Å)	0.007	0.011
Angle RMSD (°)	1.1	1.5

[a] Numbers in parentheses are for the highest resolution shell. [b] $R_{sym} = \sum_{hkl}\left|I-\langle I\rangle\right| \Big/ \sum_{hkl} I$.

[c] $R_{cryst} = \sum_{hkl}\left\|F_{(obs)}\right|-\left|F_{(calc)}\right\| \Big/ \sum_{hkl}\left|F_{(obs)}\right|$. [d] $R_{free} = R_{cryst}$ for a random 5% (MLXBIR3SG) or 10% (cXBIR3CS) of reflections.

Table S2. Summary of clinical pharmacokinetics parameters for Compound **1** from Day 1 of Cycle 1

Cohort	Dose (mg/kg)		Terminal Half-Life (hr)	C_{max} (μM)	AUC_{∞} (μM·hr)	CL (mL/min/kg)	V_{ss} (L/kg)
1	0.049	N	2	2	2	2	2
		Mean	3.8	0.18	0.13	20	1.0
		CV%	40	6.5	10	21	12
2	0.1	N	3	3	3	3	3
		Mean	4.4	0.55	0.36	10.8	0.6
		CV%	28	67	44	40	62
3	0.2	N	4	4	4	4	4
		Mean	4.2	1.1	0.84	10.7	0.7
		CV%	11	24	25	35	51
4	0.28	N	3	3	3	3	3
		Mean	3.4	1.4	1.2	12.0	0.6
		CV%	15	35	28	17	22
5	0.39	N	5	5	5	5	5
		Mean	4.0	1.6	1.4	12.2	0.8
		CV%	12	33	37	36	34
6	0.54	N	4	4	4	4	4
		Mean	3.9	3.6	2.7	10.3	0.6
		CV%	7	101	65	55	72
7	0.76	N	11	11	11	11	11
		Mean	4.1	3.3	2.8	11.6	0.7
		CV%	10	27	23	22	40
8	1.06	N	3	3	3	3	3
		Mean	3.7	6.3	5.2	10.2	0.7
		CV%	10	67	42	42	47
9	1.48	N	1	1	1	1	1
		Mean	3.9	7.0	6.8	11.3	0.8
		CV%	na	na	na	na	na

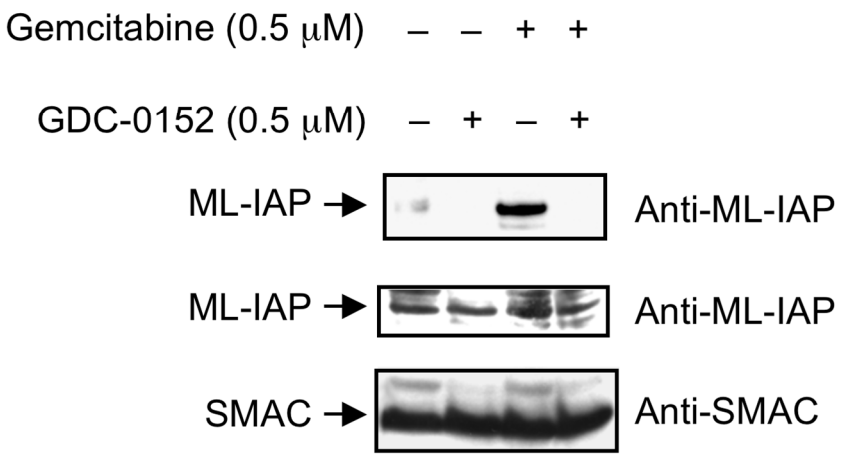

Figure S1. SK-MEL28 cells were treated with Gemcitabine (0.5 μM) and compound **1** (0.5 μM) for 20 h in the presence of the caspase inhibitor, zVAD (10 μM). At that time the cells were lysed in NP40 lysis buffer, immunoprecipitated with the anti-Smac antibody, resolved on SDS-PAGE, and immunoprecipitates (top panel) and total cell lysates (bottom two panels) were immuno-blotted with anti-ML-IAP and anti-Smac antibodies.