Abstract #345

Pediatric Preclinical Testing Program (PPTP)
Stage 1 Evaluation of Eribulin

Malcolm A. Smith[1], Min Kang[2], C. Patrick Reynolds[2], Richard B. Lock[3], Hernan Carol[3], Richard Gorlick[4], E. Anders Kolb[5], John M. Maris[6], Stephen T. Keir[7], Catherine A. Billups[8], Raushan T. Kurmasheva[9], Peter J. Houghton[9]
[1]CTEP/NCI , [2]Texas Tech University Health Science Center, [3]Children's Cancer Inst., Australia, [4]Children's Hospital at Montefiore, [5]A.I. duPont Hospital, [6]Children's Hospital of Philadelphia, [7]Duke University [8]St. Jude Children's Research Hospital, [9]Nationwide Children's Hospital

ERIBULIN

- Eribulin is a pharmaceutically and structurally optimized analog of the marine sponge natural product halichondrin B.
- Eribulin differs from both Vinca alkaloids and taxanes in its mode of binding to tubulin polymers and in its effects on microtubule dynamics.
- Its salt form, eribulin mesylate (Halaven®) is clinically used in the US, the EU, and Japan for the treatment of certain heavily pretreated patients with metastatic breast cancer, who previously received an anthracycline and a taxane.

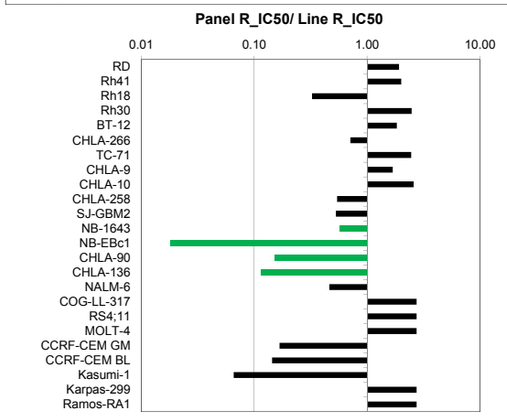
ERIBULIN *IN VITRO* ACTIVITY

- Eribulin demonstrated potent cytotoxic activity in vitro, with T/C% values approaching 0% for most cell lines at the highest concentration tested.
- The median relative IC_{50} value for the PPTP cell lines was 0.27 nM, with a range from <0.10 nM to 14.8 nM.
- The cell line panels showed distinctive median Relative In/Out% values, with the four rhabdomyosarcoma cell lines having a median value of only -38% (p=0.027 for comparison to non-rhabdomyosarcoma cell lines) and with the ALL cell lines that have a median value of -99% (p=0.005 for comparison to non-ALL cell lines).

Cell Line	Histotype	rIC_{50} (nM)	Panel rIC_{50} / Line rIC_{50}	Ymin % (Observed)	Relative In/Out%
RD	Rhabdomyosarcoma	0.14	1.92	4.49	-18%
Rh41	Rhabdomyosarcoma	0.14	2.00	6.63	-70%
Rh18	Rhabdomyosarcoma	0.83	0.33	20.92	-53%
Rh30	Rhabdomyosarcoma	0.11	2.47	12.75	-23%
BT-12	Rhabdoid	0.15	1.83	2.12	-74%
CHLA-266	Rhabdoid	0.38	0.71	5.54	-79%
TC-71	Ewing sarcoma	0.11	2.45	0.01	-99%
CHLA-9	Ewing sarcoma	0.16	1.68	1.82	-49%
CHLA-10	Ewing sarcoma	0.11	2.58	4.54	-28%
CHLA-258	Ewing sarcoma	0.50	0.54	6.29	-84%
SJ-GBM2	Glioblastoma	0.51	0.53	0.46	-95%
NB-1643	Neuroblastoma	0.47	0.57	0.53	-97%
NB-EBc1	Neuroblastoma	14.80	0.02	1.76	-92%
CHLA-90	Neuroblastoma	1.77	0.15	9.26	-67%
CHLA-136	Neuroblastoma	2.37	0.11	9.96	-65%
NALM-6	ALL	0.59	0.46	0.03	-99%
COG-LL-317	ALL	<0.10	>2.74	0.03	-99%
RS4;11	ALL	<0.10	>2.74	0.22	-99%
MOLT-4	ALL	<0.10	>2.74	0.05	-99%
CCRF-CEM (1)	ALL	1.62	0.17	0.01	-100%
CCRF-CEM (2)	ALL	1.88	0.14	0.02	-100%
Kasumi-1	AML	4.11	0.07	3.92	-86%
Karpas-299	ALCL	<0.10	>2.74	0.03	-100%
Ramos-RA1	NHL	<0.10	>2.74	0.00	-100%
Median		0.27	1.20	1.79	-89%
Minimum		0.01	0.02	0.00	-100%
Maximum		14.80	>2.74	20.92	-18%

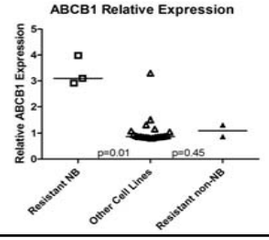
ERIBULIN COMPARE-LIKE GRAPH

- The rIC_{50} for the neuroblastoma cell lines was higher than that of the other PPTP cell lines (2.07 nM versus 0.14 nM, respectively, p=0.02), as illustrated by the green bars to the left in the COMPARE-like graph below.
- The most sensitive cell lines, each with rIC_{50} values < 0.1 nM, were all of lymphoid origin (3 ALL, 1 ALCL, and 1 NHL), shown in the graph by bars to the right. .



ERIBULIN ACTIVITY AND ABCB1 EXPRESSION

- Cell lines with ABCB1 relative expression ≥ 2-fold above the median panel expression had rIC_{50} values (2.07 nM) greater than cell lines with low expression (0.15 nM) (p=0.01).
- 3 neuroblastoma cell lines with rIC_{50} values to eribulin > 1 nM showed significantly higher ABCB1 expression than cell lines with rIC_{50} < 1 nM. Non-neuroblastoma cell lines with rIC_{50} > 1 nM did not show elevated ABCB1 expression, suggesting non-ABCB1-mediated resistance mechanisms for these lines.



ERIBULIN *IN VIVO* ACTIVITY

Line	Tumor Type	P-value	EFS T/C	Median RTV/CD45 at End of Study	Group Response
BT-29	Rhabdoid	**0.012**	> 1.6	>4	PD2
KT-16	Rhabdoid	0.865	1.1	>4	PD1
KT-10	Wilms	**<0.001**	**> 3.7**	0.0	MCR
KT-13	Wilms	**<0.001**	**> 3.3**	1.1	PR
SK-NEP-1	Ewing	**<0.001**	**> 4.3**	0.0	MCR
EW5	Ewing	**<0.001**	**3.3**	>4	PD2
EW8	Ewing	**<0.001**	**> 3.1**	0.0	MCR
TC-71	Ewing	**<0.001**	> 1.5	2.3	CR
CHLA258	Ewing	**<0.001**	**> 4.2**	0.0	MCR
Rh10	ALV RMS	**<0.001**	**> 3.8**	0.0	MCR
Rh28	ALV RMS	**<0.001**	**> 2.4**	0.0	MCR
Rh30	ALV RMS	**<0.001**	**> 3.8**	0.0	MCR
Rh30R	ALV RMS	**<0.001**	**> 4.3**	0.0	MCR
Rh41	ALV RMS	**<0.001**	**> 3.0**	0.0	MCR
Rh18	EMB RMS	**0.001**	**> 3.2**	1.8	PD2
Rh36	EMB RMS	**<0.001**	**> 6.3**	0.0	MCR
BT-28	Medulloblastoma	**<0.001**	**> 3.3**	0.7	SD
BT-50	Medulloblastoma	0.444	> 1.1	>4	PD1
BT-41	Ependymoma	1.000	.	1.3	SD
GBM2	Glioblastoma	**0.012**	**> 3.5**	0.6	MCR
BT-39	Glioblastoma	**0.045**	**> 3.6**	0.5	SD
D645	Glioblastoma	**<0.001**	**> 7.1**	3.8	CR
D456	Glioblastoma	**<0.001**	**3.4**	>4	PD2
NB-SD	Neuroblastoma	**<0.001**	**2.4**	>4	PD2
NB-1771	Neuroblastoma	**<0.001**	2.0	>4	PD2
NB-1691	Neuroblastoma	0.953	1.1	>4	PD1
NB-EBc1	Neuroblastoma	0.207	1.1	>4	PD1
CHLA-79	Neuroblastoma	0.360	1.9	>4	PD2
NB-1643	Neuroblastoma	**<0.001**	**> 4.7**	0.6	CR
OS-1	Osteosarcoma	**<0.001**	> 1.5	0.4	MCR
OS-2	Osteosarcoma	**<0.001**	**> 2.5**	0.8	SD
OS-17	Osteosarcoma	**<0.001**	**> 2.3**	0.5	CR
OS-9	Osteosarcoma	**<0.001**	1.4	>4	PD1
OS-33	Osteosarcoma	**<0.001**	**> 2.7**	0.2	MCR
OS-31	Osteosarcoma	**<0.001**	**> 2.6**	1.8	PD2
ALL-2	ALL B-precursor	**<0.001**	**> 2.8**	0.0	MCR
ALL-4	ALL B-precursor	**<0.001**	**> 4.3**	0.0	MCR
ALL-7	ALL B-precursor	**0.009**	**> 4.4**	3.0	CR
ALL-8	ALL T-cell	**<0.001**	**> 7.9**	0.0	MCR
ALL-17	ALL B-precursor	**0.001**	**> 5.3**	0.0	MCR
ALL-19	ALL B-precursor	**<0.001**	**> 8.4**	0.0	MCR
ALL-31	T-cell ALL	**<0.001**	**> 3.7**	12.9	CR
MLL-7	ALL (MLL)	**<0.001**	**> 4.7**	0.0	MCR

- **PD1 (Progressive Disease 1):** >25% ↑ in tumor volume, TGD value ≤1.5;
- **PD2 (Progressive Disease 2):** >25% ↑ in tumor volume, TGD value >1.5;
- **SD (Stable Disease):** <25% ↑ in tumor volume, <50% regression;
- **PR (Partial response):** a tumor volume regression ≥50% for at least one time point but with measurable tumor (≥ 0.10 cm^3).
- **CR (Complete response):** disappearance of measurable tumor mass (< 0.10 cm^3) for at least one time point. A complete response was considered **maintained (MCR)** if the tumor volume was <0.10 cm^3 at the end of the study period.
- **Blue shading highlights xenografts that have EFS T/C > 2.0**

Eribulin was provided for testing by Eisai Pharmaceuticals.
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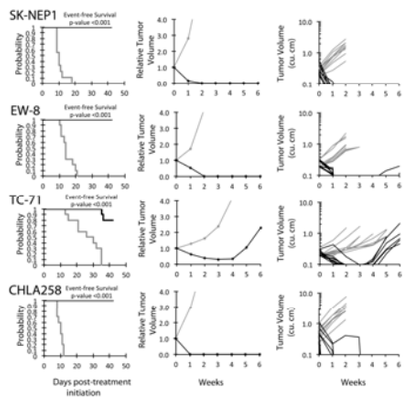
- Eribulin in vivo activity for Ewing sarcoma models is shown in the figures to the right.
- Kaplan-Meier curves for EFS (left), median relative tumor volume graphs (center), and individual tumor volume graphs (right) are shown for selected lines.
- Controls (gray lines); Treated (black lines), statistical significance (p values) of the difference between treated and control groups are included.
- Four of 5 Ewing xenografts showed CR/MCR to eribulin, while none of these same xenografts showed objective responses to vincristine.



IN VIVO RESULTS AND CONCLUSIONS

- Eribulin was tested at 1 mg/kg using a q4dx3 schedule repeated at day 21. It was well tolerated with only a 1.5% toxicity rate in the treated groups, not much higher than that observed for control animals (0.2%).
- Eribulin was highly active against a range of pediatric solid tumor and ALL xenografts, with objective responses observed in 18 of 35 (51%) solid tumor xenografts and 8 of 8 ALL xenografts.
- CR or MCR were observed in 1 of 2 Wilms tumor, 4 of 5 Ewing, 6 of 7 rhabdomyosarcoma, 2 of 4 glioblastoma, and 3 of 6 osteosarcoma xenografts. For the ALL panel, all 8 xenografts achieved CR or MCR.
- The overall activity profile of eribulin is similar to that for vincristine, but with eribulin appearing more active than vincristine for Ewing sarcoma (see above) and rhabdomyosarcoma (6 of 7 MCR for eribulin versus 2 MCR and 1 PR out of 7 for vincristine). Both vincristine and eribulin show reduced activity against neuroblastoma xenografts, perhaps related to ABCB1 expression among neuroblastoma models.
- Published eribulin pharmacokinetic data suggest that murine (CF-1 strain) exposure at 1 mg/kg administered IV and human exposure at 1.4 mg/m^2 (the recommended phase 2 dose) are reasonably comparable.
- These results support evaluation of eribulin in children with relapsed/refractory cancers, and if robust single agent activity is observed then proceeding with further development for the cancers identified as clinically responsive.