#2767 Pediatric Preclinical Testing Program (PPTP) Stage 1 Evaluation of the Antimicrotubule Agents Cabazitaxel and Docetaxel

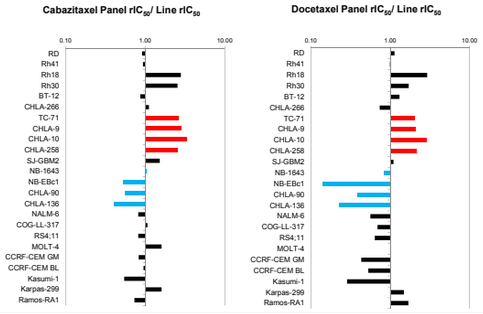
Peter J. Houghton[1], Min Kang[2], C. Patrick Reynolds[2], Richard B. Lock[3], Hernan Carol[3], Richard Gorlick[4], E. Anders Kolb[5], John M. Maris[6], Stephen T. Keir[7], Catherine A. Billups[8], Raushan T. Kurmasheva[1], Malcolm A. Smith[9]
[1]Nationwide Children's Hospital, [2]Texas Tech University 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] CTEP/NCI

CABAZITAXEL

- Cabazitaxel is a dimethoxy derivative of docetaxel that like other taxanes stabilizes microtubules against cold-induced depolymerization.
- Cabazitaxel is more potent than docetaxel against P-glycoprotein 1 (P-gp) expressing tumor cells.
- Cabazitaxel is FDA-approved for use in combination with prednisone for treatment of patients with metastatic hormone-refractory prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen.

CABAZITAXEL IN VITRO ACTIVITY

- The median relative IC_{50} (rIC_{50}) for cabazitaxel against the PPTP cell lines was 0.47 nM (range 0.14 nM to 1.16 nM), while the rIC_{50} for docetaxel was 0.88 nM (range 0.30 nM to 6.15 nM).
- For some cell lines, the maximal effect to both agents was complete cytotoxicity (Relative In/Out% value of -100%), while for other cell lines there was a plateau effect consistent with some degree of cytostasis (Relative In/Out% value of ~ 0%).
- The rIC_{50} values and the Relative In/Out% values for cabazitaxel and docetaxel were significantly correlated (R^2 = 0.64 and 0.99, respectively)
- The median rIC_{50} value for cabazitaxel for Ewing cell lines (0.17 nM) was significantly lower than that of non-Ewing cell lines (0.51 nM) (p=0.01).
- The median rIC_{50} for cabazitaxel for neuroblastoma lines (0.87 nM) was significantly greater than that of non-neuroblastoma cell lines (0.43 nM) (p=0.02).
- The COMPARE-like graphs below illustrate the relative sensitivity patterns for both cabazitaxel and docetaxel (red = Ewing and blue = neuroblastoma).



PPTP IN VITRO & IN VIVO TESTING METHODS

In vitro: In vitro testing was performed using DIMSCAN, a semiautomatic fluorescence-based digital image microscopy system that quantifies viable (using fluorescein diacetate [FDA]) cell numbers in tissue culture multiwell plates (Kang MH, et al. Pediatr Blood Cancer 56:239-249, 2011). Testing was for 96 hours at concentrations from 0.01 nM to 0.1 μM with replicates of 6-12 per data point. Data were analyzed by fitting a non-linear regression model-sigmoidal dose-response model to the response-relative fluorescence values vs. the concentration.

In vivo: Standard PPTP methods for in vivo testing were employed (http://pptp.nchresearch.org/documents/detailedAnalysisMethods.pdf).

Cabazitaxel and docetaxel were tested in vivo using a dose of 7.5 or 10 mg/kg administered by the intravenous route every 4 days x 3.

For each xenograft line, 10 mice bearing SC tumors initiated treatment when the tumors were between 0.2–0.5 cm^3. Two perpendicular tumor diameters were measured at either once or twice weekly intervals with digital vernier calipers Assuming tumors to be spherical, volumes were calculated from the formula $(\pi/6) \times d3$, where d represents the mean diameter.

The primary activity measures were the objective response measure (see legend to figure at right) and the EFS T/C measure. The EFS T/C value is defined by the ratio of the median time to event of the treatment group and the median time to event of the respective control group.

Cabazitaxel & Docetaxel in Vitro Activity against PPTP cell lines

		Cabazitaxel			Docetaxel		
Cell Line	Histotype	rIC_{50} (nM)	Ymin (Observed)	Relative In/Out (Observed Ymin)	rIC_{50} (nM)	Ymin (Observed)	Relative In/Out (Observed Ymin)
RD	Rhabdomyosarcoma	0.51	9.9	5%	0.77	8.08	3%
Rh41	Rhabdomyosarcoma	0.50	6.8	-69%	0.89	7.09	-68%
Rh18	Rhabdomyosarcoma	0.17	51.4	12%	0.30	50.00	10%
Rh30	Rhabdomyosarcoma	0.18	15.0	-9%	0.51	15.26	-8%
BT-12	Rhabdoid	0.54	4.9	-40%	0.67	4.95	-40%
CHLA-266	Rhabdoid	0.42	21.5	-18%	1.19	19.43	-26%
TC-71	Ewing sarcoma	0.18	0.1	-95%	0.44	0.03	-98%
CHLA-9	Ewing sarcoma	0.17	2.5	-30%	0.42	1.76	-51%
CHLA-10	Ewing sarcoma	0.14	4.7	-25%	0.31	3.13	-50%
CHLA-258	Ewing sarcoma	0.18	15.5	-60%	0.41	15.23	-61%
SJ-GBM2	Glioblastoma	0.31	5.2	-47%	0.80	4.07	-59%
NB-1643	Neuroblastoma	0.45	1.9	-91%	1.05	2.19	-90%
NB-EBc1	Neuroblastoma	0.89	3.8	-83%	6.15	3.53	-85%
CHLA-90	Neuroblastoma	0.84	12.2	-56%	2.23	11.48	-59%
CHLA-136	Neuroblastoma	1.16	11.4	-60%	3.84	10.16	-65%
NALM-6	ALL	0.57	0.0	-99%	1.57	0.06	-98%
COG-LL-317	ALL	0.44	0.0	-100%	1.27	0.02	-100%
RS4;11	ALL	0.57	1.3	-91%	1.38	1.40	-91%
MOLT-4	ALL	0.29	0.2	-98%	0.87	0.06	-99%
CCRF-CEM (1)	ALL	0.57	0.2	-96%	2.04	0.22	-96%
CCRF-CEM (2)	ALL	0.49	0.1	-98%	1.66	0.12	-98%
Kasumi-1	AML	0.86	8.1	-72%	3.08	7.76	-73%
Karpas-299	ALCL	0.29	4.2	-46%	0.59	4.31	-45%
Ramos-RA1	NHL	0.64	0.0	-100%	0.52	0.00	-100%
Median		**0.47**	**4.5**	**-65%**	**0.88**	**3.80**	**-66%**
Minimum		**0.14**	**0.0**	**-100%**	**0.30**	**0.00**	**-100%**
Maximum		**1.16**	**51.4**	**12%**	**6.15**	**50.00**	**10%**

Cabazitaxel was provided for testing by Sanofi.

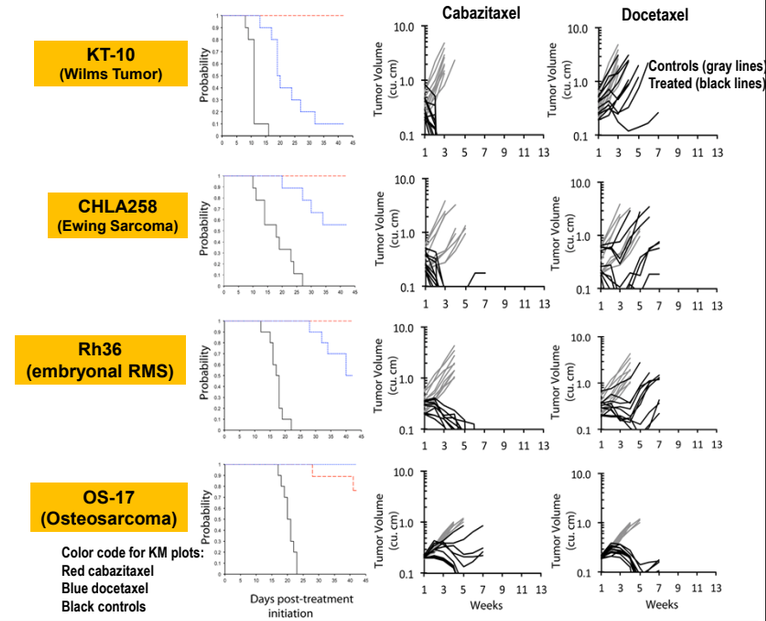
CABAZITAXEL IN VIVO ACTIVITY

In Vivo Activity of Cabazitaxel and Docetaxel against PPTP Solid Tumor Xenograft Models

Line Description	Agent	Tumor Type	EFS T/C	Median Final RTV	P-value[1]	P-value[2]	Median Group Response
KT-10	CAB	Wilms	> 3.9	0.0	<0.001	<0.001	MCR
KT-10	DOC	Wilms	1.8	>4	<0.001		PD2
SK-NEP-1	CAB	Ewing	> 3.8	0.0	<0.001	0.211	MCR
SK-NEP-1	DOC	Ewing	> 3.8	0.0	<0.001		MCR
CHLA258	CAB	Ewing	> 2.3	0.0	<0.001	0.033	MCR
CHLA258	DOC	Ewing	> 2.3	3.8	<0.001		PR
Rh30R	CAB	ALV RMS	> 3.3	0.5	<0.001	<0.001	SD
Rh30R	DOC	ALV RMS	2.4	>4	<0.001		PD2
Rh18	CAB	EMB RMS	1.6	>4	<0.001	0.147	PD2
Rh18	DOC	EMB RMS	1.3	>4	0.027		PD1
Rh36	CAB	EMB RMS	> 2.4	0.0	<0.001	0.033	MCR
Rh36	DOC	EMB RMS	> 2.4	3.9	<0.001		PD2
OS-1	CAB	Osteosarcoma	> 1.7	1.1	<0.001	1.000	SD
OS-1	DOC	Osteosarcoma	> 1.7	1.6	<0.001		PD2
OS-17	CAB	Osteosarcoma	> 2.1	1.0	<0.001	0.195	SD
OS-17	DOC	Osteosarcoma	> 2.1	0.5	<0.001		CR
OS-33	CAB	Osteosarcoma	> 2.1	0.1	<0.001	0.552	MCR
OS-33	DOC	Osteosarcoma	> 2.1	0.9	<0.001		CR

[1] P–value for comparison of the EFS distribution of the test agent to that of the controls.
[2] P–value for comparison of the EFS distribution of docetaxel and cabazitaxel.

- Red shading in the p-value columns indicates a significant difference in EFS distribution or Tumor Volume T/C between treated and control groups.
- Shading in the EFS columns indicates xenografts that have either high (dark blue), intermediate (light blue), low (gray), or indeterminant (white) activity.
- **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%
- **CR (Complete response):** disappearance of measurable tumor mass (< 0.10 cm^3)
- **MCR (Maintained CR):** CR maintained at the last observation timepoint (Day 42)
- **EFS (event free survival):** An event was defined as a quadrupling of tumor volume from the initial tumor volume. EFS was defined as the time interval from initiation of study to the first event or to the end of the study period for tumors that did not quadruple in volume.



IN VIVO RESULTS AND CONCLUSIONS

- Cabazitaxel induced slightly greater weight loss than docetaxel in non-tumored mice when each was administered intravenously every 4 days x 3, but both were tolerated in tumor-bearing animals using this schedule with 3% and 0% mortality, respectively.
- Cabazitaxel and docetaxel induced significant differences in EFS distribution compared to control in all of the evaluable solid tumor xenografts.
- Objective responses [PR, CR, or maintained CR (MCR)] were observed in 5 of 9 solid tumor xenografts treated with cabazitaxel, with all being MCRs. MCRs were observed against multiple histotypes (Wilms tumor, Ewing sarcoma, rhabdomyosarcoma, and osteosarcoma).
- Four of 9 models treated with docetaxel showed objective responses, with only 1 of these being an MCR.
- Cabazitaxel demonstrated statistically significant superiority over docetaxel in 4 of 9 models evaluated, whereas docetaxel showed no statistical advantage in any model.
- In conclusion, cabazitaxel was more potent in vitro than docetaxel against the PPTP cell lines, and it showed greater in vivo activity, albeit with slightly greater toxicity.

Testing was supported by NCI NO1CM42216. This poster will be available at: http://pptp.nchresearch.org/presentations.html.