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Initial Testing of JNJ-26854165 (Serdemetan) by the Pediatric Preclinical Testing Program

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Abstract

JNJ-26854165 was originally developed as an activator of p53 capable of inducing apoptosis in cancer cell lines. *In vitro*, JNJ-26854165 demonstrated cytotoxic activity. The ALL cell line panel had a significantly lower median IC₅₀ (0.85 μ M) than the remaining cell lines. *In vivo* JNJ-26854165 induced significant differences in EFS distribution compared to control in 18 of 37 solid tumors and in 5 of 7 of the evaluable ALL xenografts. Objective responses were observed in 4 of 37 solid tumor xenografts, and 2 of 7 ALL xenografts achieved PR or CR. Responses were noted in xenografts with both mutant and wild-type p53.

Keywords

Preclinical Testing; Developmental Therapeutics; JNJ-26854165

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INTRODUCTION

JNJ-26854165 (Serdemetan), a novel tryptamine derivative, was developed as an activator of p53, and its initially proposed mechanism of action involved preventing the association of HDM2 with the proteasome and thereby stabilizing HDM2 substrates such as p53 [1,2]. Consistent with this proposed mechanism, JNJ-26854165 induced apoptosis in acute myeloid and lymphoid leukemia cell lines and in primary acute leukemia isolates [3]. JNJ-26854165 also demonstrated activity against p53 mutant cell lines [1–3], but how this activity could be reconciled with an HDM2-mediated mechanism of action was not clear. More recent studies point to an alternative molecular mechanism of action that is HDM2-independent (manuscript in preparation).

Previous studies have described the potential utility of HDM2 inhibitors for pediatric tumors, although these have primarily focused on Nutlin-related agents as activity probes. For example, Nutlin-3 inhibited growth of neuroblastoma cell lines, with a greater effect on lines with wild-type p53 compared to those with p53 mutations [4], and it potentiated chemotherapy-induced apoptosis in neuroblastoma cell lines [5]. Using a set of 18 cell lines and 30 primary leukemia samples, Gu, et al. observed that Nutlin-3 was selectively active against ALL cell lines and primary ALL samples with wild-type p53 [6]. Reports have noted that Nutlin-3 also shows activity against rhabdomyosarcoma, osteosarcoma and Ewing sarcoma cell lines and xenografts with wild-type p53 [7–10], and a Nutlin-related HDM2 inhibitor has entered clinical evaluation [11–13].

Because of its initially proposed novel mechanism of action, JNJ-26854165 was tested against the PPTP *in vitro* and *in vivo* tumor panels irrespective of their p53/HDM2 status. The results demonstrate significant antitumor activity that is independent of p53/HDM2 status.

MATERIALS AND METHODS

In vitro testing

In vitro testing was performed using DIMSCAN, as previously described [14]. Cells were incubated in the presence of JNJ-26854165 for 96 hours at concentrations from 1 nM to 10 μ M and analyzed as previously described [15].

In vivo tumor growth inhibition studies

CB17SC *scid*^{-/-} female mice (Taconic Farms, Germantown NY), were used to propagate subcutaneously implanted kidney/rhabdoid tumors, sarcomas (Ewing, osteosarcoma, rhabdomyosarcoma), neuroblastoma, and non-glioblastoma brain tumors, while BALB/c nu/nu mice were used for glioma models, as previously described [16]. Human leukemia cells were propagated by intravenous inoculation in female non-obese diabetic (NOD)/*scid*^{-/-} mice as described previously [17]. Female mice were used irrespective of the patient gender from which the original tumor was derived. All mice were maintained under barrier conditions and experiments were conducted using protocols and conditions approved by the institutional animal care and use committee of the appropriate consortium member. Ten mice (solid tumors) or 8 mice (leukemia models) were used in each control or treatment

group. Tumor volumes (cm³) [solid tumor xenografts] or percentages of human CD45-positive [hCD45] cells [ALL xenografts] were determined as previously described [15] and responses were determined using three activity measures as previously described [15]. An in-depth description of the analysis methods is included in the Supplemental Response Definitions section.

Statistical Methods

The exact log-rank test, as implemented using Proc StatXact for SAS®, was used to compare event-free survival distributions between treatment and control groups. P-values were two-sided and were not adjusted for multiple comparisons given the exploratory nature of the studies.

Drug Information and Formulation

JNJ-26854165 was provided to the Pediatric Preclinical Testing Program by Johnson and Johnson Pharmaceutical Research, through the Cancer Therapy Evaluation Program (NCI). Powder was mixed with 1N HCl (~ 2 molar equiv.) and 20% (w/v) solution of hydroxypropyl- β -cyclodextrin in sterile water. The resulting mixture was then vortexed, sonicated for ~ 20 minutes and vigorously stirred at room temperature overnight to ensure complete dissolution of the compound. The pH of the solution was adjusted to a final pH ~4 using 0.1N NaOH and adjusted to volume with an equal volume of sterile water. Drug was stored at room temperature. JNJ-26854165 was administered by oral gavage using a daily schedule at a dose of 20 mg/kg daily $\times$ 5 for 6 weeks. JNJ-26854165 was provided to each consortium investigator in coded vials for blinded testing.

RESULTS

JNJ-26854165 in vitro testing

JNJ-26854165 was tested against the *in vitro* cell line panel at concentrations ranging from 1.0 nM to 10.0 μ M using the PPTP's standard 96 hour exposure period. JNJ-26854165 demonstrated an activity pattern consistent with a cytotoxic effect, with T/C% values approaching 0% and with Relative In/Out% values approaching -100% for some cell lines at the highest concentration tested, particularly the leukemia and lymphoma cell lines. The median relative IC₅₀ (rel-IC₅₀) for the PPTP cell lines was 1.8 μ M, with a range of 0.3 μ M (the glioblastoma cell line GBM2) to greater than 10.0 μ M. The ALL cell line panel had a significantly lower median rel-IC₅₀ (0.85 μ M, $p=0.006$) than the remaining cell lines, while the rhabdomyosarcoma cell lines had significantly higher median rel-IC₅₀ value (5.7 μ M, $p=0.0084$) than the remaining cell lines (Table I).

JNJ-26854165 in vivo testing

JNJ-26854165 was tested against the PPTP solid tumor xenografts using a dose of 20 mg/kg administered by oral gavage daily for 5 days, repeated for 6 weeks. For the ALL panel, the same dose was initially used, but it was reduced by 25% at week 5 due to weight loss and morbidity. JNJ-26854165 was generally well tolerated, with only a 3% toxicity rate in the treated groups. A complete summary of results is provided in Supplemental Table I, including total numbers of mice, number of mice that died (or were otherwise excluded),

numbers of mice with events and average times to event, tumor growth delay, as well as numbers of responses and T/C values.

Forty-four of 45 tested xenograft models were considered evaluable for efficacy, with only a single ALL xenograft being inevaluable because of toxicity. JNJ-26854165 induced significant differences in EFS distribution compared to control in 18 of 37 (49%) of the evaluable solid tumor xenografts and in 5 of 7 (71%) of the evaluable ALL xenografts (Table II). JNJ-26854165 induced tumor growth inhibition meeting criteria for intermediate EFS T/C activity (EFS T/C value of > 2.0) in 2 of 34 (6%) and for high EFS T/C activity, where tumor volume was reduced compared to the starting tumor volume, in 4 of 34 (12%) solid tumor xenografts evaluable for this measure. Intermediate or high activity for the EFS T/C metric occurred most frequently in the glioblastoma panel (2 of 4) and was also observed for one xenograft in the osteosarcoma, Wilms, medulloblastoma, and ependymoma panels.

Objective responses were observed in 4 of 37 solid tumor xenografts, including one response each among xenografts in the Wilms tumor, ependymoma, glioblastoma, and osteosarcoma xenograft panels. Stable disease was observed for a xenograft in the medulloblastoma panel, and progressive disease with growth delay (PD2) was observed among 8 solid tumor xenografts. For the ALL panel, two xenografts achieved PR or CR. The *in vivo* testing results for the objective response measure of activity are presented in Supplemental Figure 1 in a 'heat-map' format as well as a 'COMPARE'-like format, based on the scoring criteria described in the Material and Methods and the Supplemental Response Definitions section.

DISCUSSION

The *in vitro* activity of JNJ-26854165 is notable for the apparent cytotoxic activity of the agent that was most consistently observed for the PPTP leukemia cell lines. Comparable results were obtained for adult leukemia cell lines, for which JNJ-26854165 showed sub-micromolar IC₅₀ values and for which rapid induction of apoptosis was demonstrated [3]. While most of the PPTP cell lines achieved an IC₅₀ response to JNJ-26854165, the ALL cell lines and a glioblastoma cell line were notable for their relative sensitivity. This is also consistent with prior work, in which a glioblastoma cell line (U87) as well as selected acute leukemia cell lines had IC₅₀ values less than 1.0 μM [1,3].

The *in vivo* activity of JNJ-26854165 is notable for high level activity (tumor regression and leukemia remission) against a subset of PPTP xenografts. This activity showed no histotype dependence among the solid tumor xenografts, as each example of regression occurred within a different tumor panel. Only the ALL panel showed more than one xenograft with an objective response. There was also no obvious relationship with p53 mutation status, as the solid tumor xenografts with high or intermediate EFS T/C activity and the ALL xenografts with objective response included models with both wild-type and mutant p53 (Supplemental Table II). These results are consistent with previously reported findings demonstrating that JNJ-26854165 shows activity against both p53 wild-type and p53 mutant cell lines and xenografts.

A phase 1 trial of JNJ-26854165 has been completed, with the most common dose-limiting toxicity being Grade-3 QTc prolongation [18] (and manuscript in press). The agent did not proceed to phase 2 evaluation and is no longer under clinical development. The pattern of activity for JNJ-26854165 is distinctive, as the induction of complete regressions for GBM2 and OS-31 in the absence of regressions for rhabdomyosarcoma and Ewing sarcoma xenografts has not been observed for other agents evaluated by the PPTP. The mechanism of action of JNJ-26854165 likely involves effects beyond those related to MDM2 and p53 [3]. The distinctive pattern of activity for JNJ-26854165 against the selected PPTP xenografts suggests that further studies to clarify its mechanism of action may point to novel therapeutic targets for these diagnoses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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In Vitro Activity of JNJ-26854165**Table 1**

Cell Line	Histotype	Rel IC ₅₀ (μM)	Panel Rel IC ₅₀ / Line Rel IC ₅₀	Observed Ymin (%)	Model Ymin (%)	Relative In/Out%*
RD	Rhabdomyosarcoma	5.0	0.31	39.7	0.0	36%
Rh41	Rhabdomyosarcoma	6.3	0.25	38.1	0.0	20%
Rh18	Rhabdomyosarcoma	>10	0.15	55.2	0.0	19%
Rh30	Rhabdomyosarcoma	4.5	0.35	29.0	0.0	15%
BT-12	Rhabdoid	2.9	0.55	11.2	0.0	3%
CHLA-266	Rhabdoid	4.5	0.35	21.4	0.0	-18%
TC-71	Ewing sarcoma	2.3	0.67	9.9	0.0	9%
CHLA-9	Ewing sarcoma	1.4	1.09	0.6	0.0	-84%
CHLA-10	Ewing sarcoma	3.0	0.52	16.6	0.0	11%
CHLA-258	Ewing sarcoma	1.1	1.43	12.8	0.0	-67%
SJ-GBM2	Glioblastoma	0.3	5.60	4.3	6.7	-56%
NB-1643	Neuroblastoma	1.1	1.44	0.7	0.0	-97%
NB-EBc1	Neuroblastoma	1.1	1.37	3.8	0.0	-83%
CHLA-90	Neuroblastoma	7.8	0.20	44.0	0.0	22%
CHLA-136	Neuroblastoma	1.7	0.91	23.7	19.6	-18%
NALM-6	ALL	1.0	1.52	0.1	0.0	-97%
COG-LL-317	ALL	0.6	2.58	0.0	0.0	-100%
RS4;11	ALL	0.7	2.33	0.5	0.0	-96%
MOLT-4	ALL	0.6	2.61	0.0	0.0	-100%
CCRF-CEM (1)	ALL	1.2	1.30	2.6	0.0	-58%
CCRF-CEM (2)	ALL	1.5	1.03	5.7	0.0	-9%
Kasumi-1	AML	1.6	0.98	0.0	0.0	-100%
Karpas-299	ALCL	3.0	0.53	13.7	0.0	6%
Ramos-RA1	NHL	1.4	1.16	1.3	0.0	0%
Median		1.6	1.00	7.8	0.0	-18%
Minimum		0.3	0.15	0.0	0.0	-100%

Cell Line	Histotype	Rel IC ₅₀ (μM)	Panel Rel IC ₅₀ / Line Rel IC ₅₀	Observed Ymin (%)	Model Ymin (%)	Relative In/Out%*
Maximum		>10	5.60	55.2	19.6	36%

* Calculated using Observed Ymin% values.

Summary of *In Vivo* Activity of JNJ-26854165**Table II**

Line Description	Tumor Type	Estimate of Median Time to Event	P-value	EFS T/C	Median RTV/hCD45 at end of study	Tumor Volume T/C	Median Group Response	EFS Activity
KT-14	Rhabdoid	> EP	0.008	> 1.8	>4	0.67	PD2	NE
KT-12	Rhabdoid	8.5	0.1	1.3	>4	0.85	PD1	Low
KT-10	Wilms	> EP	<0.001	> 3.5	0.3	0.11	CR	High
KT-11	Wilms	16.5	0.416	1.1	>4	0.7	PD1	Low
KT-13	Wilms	19.8	0.769	1	>4	1.14	PD1	Low
SK-NEP-1	Ewing	8.8	0.746	1.1	>4	0.8	PD1	Low
EW5	Ewing	13.4	0.554	1.1	>4	0.92	PD1	Low
EW8	Ewing	18.6	0.001	1.5	>4	0.56	PD1	Low
TC-71	Ewing	6.7	0.7	0.9	>4	1.17	PD1	Low
CHLA258	Ewing	23.5	0.009	1.3	>4	0.69	PD1	Low
Rh10	ALV RMS	> EP	<0.001	> 1.5	3.4	0.62	PD2	NE
Rh28	ALV RMS	20.1	0.864	1.2	>4	0.71	PD1	Low
Rh30	ALV RMS	19.6	<0.001	2	>4	0.5	PD2	Low
Rh30R	ALV RMS	12.6	0.227	1.1	>4	0.88	PD1	Low
Rh41	ALV RMS	13.5	0.495	1.3	>4	0.78	PD1	Low
Rh18	EMB RMS	21.8	0.016	1.4	>4	0.74	PD1	Low
BT-28	Medulloblastoma	6.3	0.045	1.4	>4	0.7	PD1	Low
BT-45	Medulloblastoma	> EP	<0.001	> 2.3	0.9	0.58	SD	High
BT-50	Medulloblastoma	33.4	0.002	0.9	>4	0.97	PD1	Low
BT-41	Ependymoma	> EP	<0.001	> 1.7	1.7	0.52	PD2	NE
BT-44	Ependymoma	> EP	<0.001	> 3.2	0.4	0.75	PR	High
GBM2	Glioblastoma	> EP	<0.001	> 4.0	2.8	0.09	CR	Int
BT-39	Glioblastoma	27.4	<0.001	1.8	>4	0.52	PD2	Low
D645	Glioblastoma	22.5	0.007	3.4	>4	0.66	PD2	Int
D456	Glioblastoma	10.7	0.043	1.6	>4	0.73	PD1	Low

Line Description	Tumor Type	Estimate of Median Time to Event	P-value	EFS T/C	Median RTV/hCD45 at end of study	Tumor Volume T/C	Median Group Response	EFS Activity
NB-SD	Neuroblastoma	14.3	0.913	0.9	>4	1.12	PD1	Low
NB-1771	Neuroblastoma	5	0.209	0.9	>4	1.15	PD1	Low
NB-1691	Neuroblastoma	8.1	0.463	1	>4	1.16	PD1	Low
NB-EBc1	Neuroblastoma	9.2	0.002	1.3	>4	0.7	PD1	Low
CHLA-79	Neuroblastoma	15.3	0.283	2.3	>4	0.57	PD2	Low
NB-1643	Neuroblastoma	8.8	0.547	1	>4	0.91	PD1	Low
OS-1	Osteosarcoma	37	<0.001	1.8	>4	0.59	PD2	Low
OS-2	Osteosarcoma	24.3	0.164	1.2	>4	0.91	PD1	Low
OS-17	Osteosarcoma	15.7	0.854	1	>4	1.04	PD1	Low
OS-9	Osteosarcoma	22.2	0.361	1	>4	1.04	PD1	Low
OS-33	Osteosarcoma	16.4	0.515	1	>4	0.83	PD1	Low
OS-31	Osteosarcoma	> EP	<0.001	> 2.8	0.3	0.4	MCR	High
ALL-2	ALL B-precursor	27.2	0.005	1.5	>25	.	PD2	Low
ALL-3	ALL B-precursor	39.8	0.001	5.8	>25	.	PR	Int
ALL-4	ALL B-precursor	3.8	0.786	1.1	>25	.	PD1	Low
ALL-7	ALL B-precursor	17.6	<0.001	3.2	>25	.	PD2	Int
ALL-8	ALL T-cell	7	0.45	0.8	>25	.	PD1	Low
ALL-16	ALL T-cell	30.8	0.133	2.1	>25	.	SD	Low
ALL-17	ALL B-precursor	> EP	<0.001	> 4.3	1.5	.	CR	Int
ALL-19	ALL B-precursor	21.4	0.009	4.2	>25	.	PD2	Int

Bold font indicates xenografts with significant differences in EFS distribution or with SD, PR, CR, or MCR objective responses.