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# Initial Testing (Stage 1) of LCL161, a SMAC Mimetic, by the Pediatric Preclinical Testing Program

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## Abstract

LCL161, a SMAC mimetic, was tested against the PPTP *in vitro* panel (1.0 nM to 10.0 μM) and the PPTP *in vivo* panels (30 mg/kg or 75 mg/kg [solid tumors] or 100 mg/kg [ALL]) administered orally twice weekly. LCL161 showed a median relative $IC_{50}$ value of >10 μM, being more potent against several leukemia and lymphoma lines. *In vivo* LCL161 induced significant differences in EFS distribution in approximately one-third of solid tumor xenografts (osteosarcoma, glioblastoma), but in no ALL xenografts. No objective tumor responses were observed. *In vivo* LCL161 demonstrated limited single agent activity against the pediatric preclinical models studied.

### Keywords

Preclinical Testing; Developmental Therapeutics; SMAC mimetic

## INTRODUCTION

The process of apoptosis plays a critical role in the development and homeostasis of multicellular organisms. In many cancers the cell death machinery is inhibited by the upregulation of antiapoptotic proteins, suggesting that the restoration of apoptotic activity might be an effective approach for treating these cancers. Members of the inhibitor of

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apoptosis (IAP) family of proteins are upregulated in many cancers, and they initially were thought to primarily contribute to oncogenesis through their ability to directly inhibit members of the caspase family of apoptotic enzymes. It now appears that only one member of the family (XIAP) acts as a direct inhibitor of caspases [1], and that it is able to inhibit the enzymatic activity of both initiator (caspase-9) and executor (caspase-3 and -7) caspases. A more recently recognized oncogenic role for IAP family members is in regulating NF-κB signaling [2].

The second mitochondria-derived activator of caspases (Smac) has a unique function in regulating apoptosis. In non-stressed cells Smac is sequestered in mitochondria and is released into the cytosol only upon induction of mitochondrial dysfunction or apoptosis [3,4]. Cytosolic Smac selectively binds to IAPs through conserved *Baculovirus* IAP Repeat (BIR) domains [5,6], promoting cell death. Consequently, small molecule drugs that mimic the interaction of Smac with IAPs (Smac mimetics) have been designed. Smac mimetics bind with high affinity to IAPs, including XIAP, cIAP1 and cIAP2. Surprisingly, cell death induced by Smac mimetics was found to require TNFα signaling and caspase-8 and to be independent of caspase-9 [7]. Work from a number of laboratories has shown that Smac mimetics rapidly induce auto-ubiquitylation and proteasomal degradation of cIAP1 and cIAP2 resulting in the activation of non-canonical NF-κB signaling and subsequent increased TNFα production and autocrine stimulation of TNFR1 [7–10]. This increased TNFα signaling leads to caspase-8 activation and apoptosis as a result of the enhanced RIPK1 levels that are a downstream effect of reduced cIAP ubiquitylation of RIPK1 [8–10].

LCL161 is a small molecule drug mimetic of Smac that binds to IAPs with high affinity and initiates the destruction of cIAP1 and cIAP2 [11]. LCL161 induces apoptosis in some cancer cell lines and potentiates the effects of tyrosine kinase inhibition against leukemic disease [11,12]. LCL161 is currently in clinical trials as a single agent or in combination with cytotoxic agents [13].

## MATERIALS AND METHODS

### *In vitro* testing

*In vitro* testing was performed using DIMSCAN, as previously described [14]. Cells were incubated in the presence of LCL161 for 96 hours at concentrations from 1 nM to 10 μM 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 [16,17]. Human leukemia cells were propagated by intravenous inoculation in female non-obese diabetic (NOD)/*scid*$^{-/-}$ mice as described previously [18]. 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. Eight to ten mice were used in each control or treatment group. Tumor volumes ($cm^3$) [solid tumor xenografts] or percentages of human CD45-positive [hCD45] cells [ALL xenografts] were determined as previously described [16]. Responses were determined using three activity measures as previously described [16]. 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.

### Drugs and Formulation

LCL161 was provided to the Pediatric Preclinical Testing Program by Novartis Pharmaceuticals, through the Cancer Therapy Evaluation Program (NCI). LCL161 was tested initially using a 30 mg/kg dose administered by oral gavage twice weekly (Mon-Tues) repeated weekly for a planned treatment duration of 6 weeks. Subsequently, limited testing at 75 mg/kg (solid tumors) or 100 mg/kg (ALL models) was undertaken using the same schedule and route of drug administration. LCL161 was formulated for oral gavage by dissolving in 0.1N HCl, and diluting to volume with sodium acetate buffer (100 mM, pH 4.63) to produce a solution with pH 4.3–4.6. LCL161 was provided to each consortium investigator in coded vials for blinded testing.

## RESULTS

### In vitro testing

LCL161 was evaluated against the the 23 cell lines in the PPTP *in vitro* panel using 96 hour exposure to concentrations ranging from 1.0 nM to 10.0 μM. LCL161 achieved 50% growth inhibition (i.e., Ymin < 50%) against only 3 of the 23 tested PPTP cell lines, Table I. The three cell lines included two T-cell ALL cell lines (COG-LL-317 and CCRF-CEM) and an anaplastic large cell lymphoma cell line (Karpas-299), with CCRF-CEM and Karpas-299 showing the lowest relative $IC_{50}$ values (0.25 and 1.6 μM, respectively).

### In vivo testing

LCL161 was tested using a 30 mg/kg dose administered by oral gavage twice weekly (Mon-Tues) repeated weekly for a planned treatment duration of 6 weeks. The dose was reduced below the planned 100 mg/kg dose because of the results of toxicity testing in SCID mice. However, toxicity in tumored mice was similar in control and treatment groups (1.6%). All 46 tested xenograft models were considered evaluable for efficacy. Complete details of testing are provided in Supplemental Tables I and II, 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.

LCL161 induced significant differences in EFS distribution compared to controls in 12 of 38 evaluable solid tumor xenografts (32%) tested. Significant tumor growth delay was observed in multiple solid tumor panels, but was most consistently present in the osteosarcoma (5 of 6), glioblastoma (2 of 4) and neuroblastoma (2 of 6) panels. None of the 8 evaluable ALL xenografts showed a significant difference in EFS distribution between treated and control animals.

Criteria for intermediate activity for the time to event activity measure (i.e., EFS T/C > 2) were met in 1 of 36 (3%) solid tumor xenografts evaluable for this measure (Table II). Intermediate activity was observed for the medulloblastoma xenograft BT-28. No ALL xenografts met criteria for intermediate activity for the EFS T/C activity measure. Using the PPTP Objective Response Measure, objective response (i.e., tumor regression) was scored for a single xenograft, BT-28 (medulloblastoma). However, responses in individual animals were widely divergent for this xenograft, with 5 tumors regressing completely and four

tumors progressing (PD1), giving a median `score' consistent with PR. Among the remaining solid tumor xenografts, 5 showed a PD2 response (progressive disease with growth delay). PD2 responses occurred across multiple panels. There were no objective responses (PR or CR) among the ALL xenografts.

Because of the limited toxicity observed in the initial testing at 30 mg/kg, LCL161 was re-tested at higher doses against selected solid tumor models (75 mg/kg) and ALL models (100 mg/kg) using the same schedule of drug administration. LCL161 was well tolerated at this higher dose (1 of 60 deaths in treatment groups). Against EW-5 and BT-39 glioblastoma LCL161 significantly inhibited growth, whereas against BT-28 tumors LCL161 did not significantly inhibit growth (PD1 responses), and hence did not confirm the PR at the lower dose level. LCL161 was ineffective against ALL 7 (B-precursor), ALL 19 (T-cell), ALL 31 (T-cell) and MLL 7 (B-precursor) leukemia models (Table II). The anaplastic large cell lymphoma line, Karpas-299, was the most sensitive cell line in the *in vitro* panel, and hence we tested its sensitivity (75 mg/kg dose level) *in vivo* maintained as a subcutaneous xenograft. LCL161 significantly inhibited growth of the Karpas-299 xenograft with an EFS T/C value of 1.6, but tumor regression was not observed (Table II).

## DISCUSSION

The limited level of *in vitro* activity observed for LCL161 by the PPTP is consistent with results for adult cancer cell lines showing that LCL161 demonstrates activity against a minority of cell lines [11]. However, while some adult cancer cell lines have $IC_{50}$ values to LCL161 in the 20 to 50 nM range, there are no pediatric cell lines in the PPTP panel that show this degree of sensitivity. A report describing the activity of another small molecule SMAC-mimetic against 50 non-small cell lung cancer (NSCLC) cell lines also showed activity against a minority (approximately 15%) of cell lines [19]. Similarly, a SMAC-mimetic developed by Abbott Laboratories showed activity against approximately 15% of 59 cell lines studied [20]. The three PPTP cell lines showing the greatest sensitivity to LCL161 were all lymphoid derived: CCRF-CEM (T-cell ALL) and Karpas-299 (ALCL) and COG-LL-317 (T-cell ALL). *In vivo*, LCL161 had limited activity causing growth delay in a subset of PPTP xenografts, with a single tumor line BT-28 meeting the criteria for PR at 30 mg/kg, but that was not reproducible at 75 mg/kg. There were no objective responses in the leukemia models at either dose level evaluated. Thus, LCL161 as a single agent demonstrated a low level of activity in this screen.

An evaluation of LCL161 activity against adult cancer cell lines demonstrated that canonical and non-canonical NFκB signaling are not differentially activated in sensitive and resistant cells, but that TNFα is induced only in the former [11]. Furthermore, high baseline TNFα levels appeared to predispose to sensitivity. We therefore examined TNFα expression levels for PPTP cell lines and xenografts generated using Affymetrix U133 Plus 2.0 arrays [21] (Supplemental Figure 1). Few cell lines or xenografts showed elevated TNFα expression. One of the two most sensitive cell lines (Karpas-299) showed elevated TNFα expression, as did a glioblastoma xenograft (BT-39) that showed significant growth delay to LCL161. Multiple B-precursor ALL xenografts showed moderately elevated TNFα expression, but LCL161 did not show significant *in vivo* activity against these xenografts.

In summary, LCL161 showed limited *in vitro* and *in vivo* activity as a single agent against the PPTP's childhood cancer preclinical models. Future work evaluating small molecule Smac mimetics such as LCL161 in the childhood cancer setting can focus on their utility in combination with standard cytotoxic agents, signaling pathway inhibitors [12], and activators of the extrinsic cell death pathway such as TRAIL [22,23].

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table I**

Summary of LCL161 activity *In vitro*

| Cell Line | Histology | Relative $IC_{50}$ (μM) | Ymin % (Observed) |
|---|---|---|---|
| RD | Rhabdomyosarcoma | < 10 | 78.1 |
| Rh41 | Rhabdomyosarcoma | < 10 | 58.9 |
| Rh18 | Rhabdomyosarcoma | < 10 | 61.1 |
| Rh30 | Rhabdomyosarcoma | < 10 | 71.6 |
| BT-12 | Rhabdoid | < 10 | 86.3 |
| CHLA-266 | Rhabdoid | < 10 | 68.7 |
| TC-71 | Ewing sarcoma | < 10 | 84.0 |
| CHLA-9 | Ewing sarcoma | < 10 | 84.4 |
| CHLA-10 | Ewing sarcoma | < 10 | 64.7 |
| CHLA-258 | Ewing sarcoma | < 10 | 53.3 |
| GBM2 | Glioblastoma | < 10 | 72.4 |
| NB-1643 | Neuroblastoma | < 10 | 94.1 |
| NB-EBc1 | Neuroblastoma | < 10 | 80.5 |
| CHLA-90 | Neuroblastoma | < 10 | 73.6 |
| CHLA-136 | Neuroblastoma | < 10 | 97.0 |
| NALM-6 | ALL | < 10 | 50.6 |
| COG-LL-317 | ALL | 9.3 | 46.8 |
| RS4;11 | ALL | < 10 | 63.9 |
| MOLT-4 | ALL | < 10 | 75.3 |
| CCRF-CEM | ALL | 0.25 | 12.5 |
| Kasumi-1 | AML | < 10 | 53.4 |
| Karpas-299 | ALCL | 1.60 | 4.9 |
| Ramos-RA1 | NHL | < 10 | 52.2 |
| **Median** | | **< 10** | **68.7** |
| **Minimum** | | **0.25** | **4.9** |
| **Maximum** | | **< 10** | **97.0** |

ALCL, anaplastic large cell lymphoma.

**Table II**

Summary of LCL161 Activity *In Vivo*

| Xenograft Line | Histology | Median Time to Event | P-value | EFS T/C | Median Final RTV | T/C | P-value | T/C Activity | EFS Activity | Response Activity |
|---|---|---|---|---|---|---|---|---|---|---|
| 30 mg/kg | | | | | | | | | | |
| BT-29 | Rhabdoid | 12.5 | 0.379 | 1.0 | >4 | 0.94 | 0.481 | Low | Low | Low |
| KT-14 | Rhabdoid | 31.7 | 0.578 | 1.0 | >4 | 1.04 | 0.684 | Low | Low | Low |
| KT-12 | Rhabdoid | 10.0 | 0.465 | 1.1 | >4 | 0.79 | 0.353 | Low | Low | Low |
| KT-10 | Wilms | 14.3 | 0.701 | 0.9 | >4 | 1.09 | 0.796 | Low | Low | Low |
| KT-11 | Wilms | 11.5 | 0.518 | 1.0 | >4 | 1.16 | 0.631 | Low | Low | Low |
| KT-13 | Wilms | 10.9 | 0.093 | 1.1 | >4 | 1.07 | 0.796 | Low | Low | Low |
| SK-NEP-1 | Ewing | 9.0 | 0.310 | 1.0 | >4 | 0.81 | 0.143 | Low | Low | Low |
| EW5 | Ewing | 14.4 | <0.001 | 1.5 | >4 | 0.74 | 0.009 | Low | Low | Int |
| EW8 | Ewing | 11.7 | 0.073 | 1.8 | >4 | 0.46 | 0.165 | Low | Low | Int |
| TC-71 | Ewing | 9.7 | 0.971 | 1.0 | >4 | 1.23 | 0.853 | Low | Low | Low |
| CHLA258 | Ewing | 8.3 | 0.758 | 1.2 | >4 | 1.18 | 0.971 | Low | Low | Low |
| Rh10 | ALV RMS | 25.1 | 0.932 | 1.3 | >4 | 0.95 | 0.965 | Low | Low | Low |
| Rh28 | ALV RMS | 13.1 | 0.342 | 0.7 | >4 | 1.43 | 0.052 | Low | Low | Low |
| Rh30 | ALV RMS | 15.3 | 0.186 | 1.4 | >4 | 0.80 | 0.315 | Low | Low | Low |
| Rh30R | ALV RMS | 12.2 | 0.271 | 1.2 | >4 | 0.66 | 0.002 | Low | Low | Low |
| Rh41 | ALV RMS | 15.4 | 0.586 | 1.0 | >4 | 1.00 | 1.000 | Low | Low | Low |
| Rh18 | EMB RMS | 13.5 | <0.001 | 1.2 | >4 | 0.63 | 0.002 | Low | Low | Low |
| BT-28 | Medulloblastoma | > EP | 0.002 | >10.9 | >4 | 0.42 | 0.009 | Int | Int | High |
| BT-45 | Medulloblastoma | 21.3 | 0.051 | 1.3 | >4 | 0.66 | 0.165 | Low | Low | Low |
| BT-50 | Medulloblastoma | > EP | 0.204 | > 1.3 | 2.8 | 0.79 | 0.014 | Low | NE | Int |
| BT-41 | Ependymoma | > EP | 1.000 | . | 2.0 | 0.57 | 0.123 | Low | NE | Int |
| BT-44 | Ependymoma | 9.6 | 0.707 | 0.9 | >4 | 1.31 | 0.842 | Low | Low | Low |
| GBM2 | Glioblastoma | 9.7 | 0.709 | 0.9 | >4 | 0.97 | 0.009 | Low | Low | Low |
| BT-39 | Glioblastoma | 11.9 | 0.003 | 1.8 | >4 | 0.65 | 0.123 | Low | Low | Int |
| D645 | Glioblastoma | 9.7 | 0.120 | 0.8 | >4 | 1.19 | 0.165 | Low | Low | Low |
| D456 | Glioblastoma | 11.8 | 0.045 | 1.5 | >4 | 0.82 | 0.481 | Low | Low | Low |

| Xenograft Line | Histology | Median Time to Event | P-value | EFS T/C | Median Final RTV | T/C | P-value | T/C Activity | EFS Activity | Response Activity |
|---|---|---|---|---|---|---|---|---|---|---|
| NB-SD | Neuroblastoma | 14.9 | 0.714 | 1.4 | >4 | 0.83 | 0.008 | Low | Low | Low |
| NB-1771 | Neuroblastoma | 23.4 | 0.008 | 1.4 | >4 | 0.52 | 0.853 | Low | Low | Low |
| NB-1691 | Neuroblastoma | 10.6 | 0.454 | 1.1 | >4 | 0.90 | 0.696 | Low | Low | Low |
| NB-EBc1 | Neuroblastoma | 14.8 | 0.024 | 1.4 | >4 | 0.76 | 0.234 | Low | Low | Low |
| CHLA-79 | Neuroblastoma | 18.5 | 0.146 | 1.5 | >4 | 0.80 | 0.579 | Low | Low | Low |
| NB-1643 | Neuroblastoma | 8.6 | 0.748 | 1.0 | >4 | 1.04 | 0.035 | Low | Low | Low |
| OS-1 | Osteosarcoma | 38.8 | 0.017 | 1.3 | >4 | 0.76 | 0.001 | Low | Low | Low |
| OS-2 | Osteosarcoma | 23.6 | <0.001 | 1.3 | >4 | 0.76 | 0.278 | Low | Low | Low |
| OS-17 | Osteosarcoma | 20.8 | 0.500 | 1.0 | >4 | 0.91 | <0.001 | Low | Low | Low |
| OS-9 | Osteosarcoma | 28.6 | <0.001 | 1.8 | >4 | 0.57 | <0.001 | Low | Low | Int |
| OS-33 | Osteosarcoma | 26.1 | <0.001 | 1.4 | >4 | 0.61 | 0.133 | Low | Low | Low |
| OS-31 | Osteosarcoma | 23.5 | 0.044 | 1.1 | >4 | 0.81 | | Low | Low | Low |
| ALL-2 | ALL B-precursor | 10.4 | 0.531 | 1.0 | >25 | . | | | Low | Low |
| ALL-3 | ALL B-precursor | 9.3 | 0.363 | 1.2 | >25 | . | | | Low | Low |
| ALL-4 | ALL B-precursor | 9.0 | 0.819 | 1.5 | >25 | . | | | Low | Low |
| ALL-7 | ALL B-precursor | 6.0 | 1.000 | 1.0 | >25 | . | | | Low | Low |
| ALL-8 | ALL T-cell | 11.2 | 0.547 | 1.0 | >25 | . | | | Low | Low |
| ALL-16 | ALL T-cell | > EP | 0.103 | > 1.4 | >25 | . | | | NE | Int |
| ALL-17 | ALL B-precursor | 6.3 | 0.669 | 1.1 | >25 | . | | | Low | Low |
| ALL-19 | ALL B-precursor | 5.4 | 0.652 | 1.1 | >25 | . | | | Low | Low |
| 75 mg/kg (solid Tumors) | | | | | | | | | | |
| EW5 | Ewing | 11.5 | <0.001 | 1.7 | >4 | 0.68 | <0.001 | Low | Low | Low |
| BT-28 | Medulloblastoma | 5.7 | 0.3190 | 1.2 | >4 | 0.66 | 0'165 | Low | Low | Low |
| BT-39 | Glioblastoma | 18.1 | 0.0060 | 1.3 | >4 | 0.66 | | Low | Low | Low |
| Karpas-299 | ALCL | 13.3 | <0.001 | 1.6 | >4 | 0.65 | | Low | Low | Low |
| 100 mg/kg (ALL models) | | | | | | | | | | |
| ALL-7 | ALL B-precursor | 3.0 | 0.6880 | 1.0 | >25 | . | | | Low | Low |
| ALL-19 | ALL B-precursor | 10.2 | 0.5240 | 2.1 | >25 | . | | | Low | Low |
| ALL-31 | ALL T-cell | 5.8 | 0.4890 | 1.0 | >25 | . | | | Low | Low |

| Xenograft Line | Histology | Median Time to Event | P-value | EFS T/C | Median Final RTV | T/C | P-value | T/C Activity | EFS Activity | Response Activity |
|---|---|---|---|---|---|---|---|---|---|---|
| MLL-7 | ALL B-precursor | 8.9 | 0.2150 | 1.7 | >25 | . | | | Low | Low |