## Title

Highly Specific Inhibitor for Syk Induces Chronic Lymphocytic Leukemia Cell Apoptosis



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# Highly Specific Inhibitor for Syk Induces Chronic Lymphocytic Leukemia Cell Apoptosis,

Highly Specific Inhibitor for Syk Induces Chronic Lymphocytic Leukemia Cell Apoptosis,

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## Abstract

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The antibodies expressed by CLL cells are highly selected, implicating a role for antigen in the pathogenesis of this disease. The B-cell receptor (BCR) for antigen may become engaged by microbial or self-antigens to induce activation of downstream adapter/signaling molecules. This, either alone or in concert with activation of other receptors, can induce CLL-cell expression of genes encoding proteins involved in cell survival or proliferation, e.g. c-*MYC*, potentially enhancing the tendency for disease progression. Our prior studies found that ZAP-70 in CLL cells enhanced BCR

t for the relatively aggressive clinical behavior of patients who have

ein. Although transduction of ZAP-70-negative CLL cells with vectors

BCR signaling, we found this effect did not require an active ZAP-70

BCR signaling. As such, inhibitors of Syk could be useful therapeutically, as indicated by a clinical study demonstrating that one Syk inhibitor, fostamatinib disodium (R406/R788), has activity in the treatment of patients with this disease. However, at concentrations of fostamatinib required for clinical activity this drug also can inhibit several kinases other than Syk, including Lck, JAK, and Flt3, making it difficult to conclude that the activity of this drug solely was due to its capacity to inhibit Syk. Coffey and colleagues developed a series of highly potent and selective small molecule Syk inhibitors. One of these inhibitors, PRT060318, is a highly specific inhibitor of Syk that is more selective than fostamatinib. We examined whether this specific Syk inhibitor could affect BCR signaling and CLL-cell survival. We evaluated the effect of PRT060318 on BCR signaling by calcium influx induced through surface IgM ligation. We found that PRT060318 inhibited IgM induced BCR signaling with an $IC_{50}$~200nM. CLL cells that express ZAP-70 (n=13) or that lacked expression of this kinase (n=10) were treated with 5 μM PRT060318 and examined for cell viability 24 hours later. The average viability of CLL cells that expressed ZAP-70 was significantly lower (70.4 ± 16.1) than that of CLL cells that lacked expression of ZAP-70 (93.6 ± 9.0) ($P<0.01$), revealing that PRT060318 had greater activity in inducing apoptosis of CLL cells that had high-level expression of ZAP-70. Moreover, Syk inhibition abrogated the capacity of surface IgM ligation to enhance CLL cell survival, the viability of CLL cells treated with PRT060318 and anti-μ (38.8 ± 5.4) was significantly lower than CLL cells with anti-μ stimulation after 48 hours (64.0 ± 6.0) ($P<0.01$, n=3). PRT060318 also inhibited the capacity of marrow stromal cells to support the survival of CLL cells in vitro (35.3 ± 5.2 vs. 61.8 ± 4.7) ($P<0.01$, n=4). These results indicate that selective Syk inhibition by PRT060318 can induce apoptosis in CLL cells, has greater activity against CLL cells that express ZAP-70 and might be most active in treating patients with aggressive disease characteristics.

### Disclosures:

**Coffey:***Portola Pharmaceuticals Inc.:* Employment. **Carson:***Wintherix:* Equity Ownership. **Kipps:***Igenica:* Equity Ownership, Membership on an entity's Board of Directors or advisory committees; *Celgene:* Consultancy, Research Funding; *Abbot Industries:* Research Funding; *Pharmacyclics:* Membership on an entity's Board of Directors or advisory committees; *Genentech:* Research Funding; *GSK:* Research Funding; *Gilead Sciences:* Research Funding; *Amgen:* Research Funding.

**Topics:** adaptor signaling protein, antibodies, antigens, apoptosis, autoantigens, calcium, chronic b-cell leukemias, chronic lymphocytic leukemia, disease progression, fostamatinib

## Author notes

* Asterisk with author names denotes non-ASH members.

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Abstract