METHODS

Cell line and reagents
Mantle cell lymphoma cell lines Jeko-1, Z-138, JVM-2, MAVER-1, multiple myeloma cell lines H929 and MM1S, diffuse large B-cell lymphoma cell lines SUDHL-6 and SUDHL-10, and MTA cell lines FEPD and MAC2A were grown in RPMI medium with 10% fetal calf serum. MAC2A and MTA (PTCL) were grown in RPMI medium with 10% fetal calf serum and 1% sodium pyruvate. OCI-LY7 and OCI-LY10, VAL (DLBCL) SMZ1 (PTCL) cell lines were grown in Iscove modified Dulbecco medium with 10% fetal calf serum. Fresh medium was added every 2 to 3 days, and the cells were kept at a cell concentration of 0.1 to 1x 10⁶/mL. MDA-MB-231 and Cells were incubated at 37 ºC in a 5% CO2 atmosphere, 95% humidity in CO2 incubator.

Cell viability assays
Cell viability was evaluated using the Cell Titer-Glo Reagent (Promega) according to the manufacturer's manual, as reported previously¹. Experiments were carried out in 48-well plates, with each treatment in triplicate. Samples were taken at typically 24, 48, and 72 hours after treatment. Cell viability was expressed by the decreasing percentage of live cells in each treatment relative to the untreated control from the same experiment, as a function of time. IC₅₀ and IC₉₀, concentrations required to inhibit viability by 50% and 90%, respectively, were calculated using the Graphpad Prism software.

Purification of primary lymphoma cells
Isolation of primary lymphoma cells was conducted as described previously¹, using a protocol approved by the Institutional Review Board (IRB) of Columbia University Irving Medical Center.

Mouse xenograft model
Mouse experiments were carried out in accordance with the principles of laboratory animal care under an Institutional Animal Care and Use Committee-approved protocol at Columbia University Irving Medical Center. Four- to six-week-old SCID beige mice (Charles River Laboratories) were injected subcutaneously at the right flank with 5x10⁶ cells of the MCL cell line Z-138 suspended in 50% phosphate-buffered saline and 50% Matrigel matrix. When the tumors approached palpable size 250-300 mm³, the mice were divided into three groups of 8 mice: (i) vehicle control group, which received vehicle of 10% DMSO, 10% Tween-20, and 80% water; (ii) SR-3029 at 30 mg/kg daily and (iii) LY2409881 at 40mg/kg daily. SR3029 was prepared in a vehicle of 10% DMSO, 10% Tween-20, and 80% water. The dosing solution was to dilute the dry drug in DMSO first and mixed by inversion of the
tubes. Tween-20 and water were then added and followed by sonication in a water bath to make a uniform suspension of the solutions. The drug was administered intraperitoneally daily for 16 days. The data were expressed as average tumor volume (mm$^3$) per group as a function of time. Tumor volume was calculated using the formula: $(4/3) \pi r^3$, where $r=(\text{length}+\text{width})/4$. At day 16 or endpoint, mice were euthanized, and the tumor was isolated for further examinations.

**Protein extraction and western blotting analysis**

Cells were collected by centrifugation at 1250 rpm and then washed with ice-cold PBS twice to completely remove medium. RIPA lysis buffer (Thermo Fisher Scientific) supplemented with Halt Protease Inhibitor Cocktail (Santa Cruz Biotechnology) was added to cell pellets to extract protein. Protein concentrations in lysates were measured by Pierce BCA Protein Assay Kit (Thermo Fisher Scientific) and followed by the addition of SDS loading buffer (4X) and heated at 95˚C for 5 min. Equal amount of protein samples was subjected to SDS-PAGE and transferred to a PVDF membrane (Bio-Rad). The membrane was blocked in 5% BSA/Milk at room temperature for 1 hour and incubated with appropriate antibodies at 4˚C overnight. Antibodies were diluted in TBST (TBS with 0.1% Tween) with 5% BSA/ Milk. On the next day, the membranes were washed with TBST and incubated with appropriate secondary antibodies at room temperature for 1 hour. Membranes were developed using the chemiluminescence detection system from Thermo Scientific. Antibodies for the following proteins were purchased from Cell Signaling Technology p-4E-BP1-S65, p-4E-BP1-T70, 4E-BP1, β-catenin, p-p70SK, eIF4E, eIF4G, mTOR, RAPTOR, Lamin B1, and β-actin. Antibodies for CK1δ were purchased from Santa Cruz Biotechnology. CK1ε antibody was purchased from Abcam. Tubulin antibody was purchased from Sigma. Subcellular fractionation was performed using NE-PER nuclear and cytoplasmic extraction reagents from Thermo Scientific as per manufacturer’s protocol and fractions were subjected to western blotting. Lamin B1 and Tubulin were used as loading control for nuclear and cytoplasmic fractions respectively.

**Cap binding assay**

Cells were harvested and lysed in CAP lysis buffer (1% Triton-X, 100mM KCL, 0.1 M EDTA, 10% glycerol, 2mM MgCl2, 20mM HEPES, protease inhibitor cocktail mixture) and were incubated on ice for 5 min at 4 °C and centrifuged at 15000 rpm for 5 minutes. The cleared lysates were incubated with pre-washed GTP-sepharose or m$^7$-GTP-sepharose (or agarose) beads (AXXORA) with an additional CAP lysis buffer and incubated for 3hrs at 4 °C with occasional shaking. The beads were washed three times and proteins associated with CAP was eluted with 4X SDS loading buffer and subjected to Western blotting.
SUnSET assay
SUnSET assay was performed as per Manufacturer's protocol (Kerafast). Briefly, cells were treated and incubated for 30 minutes with 1μg/ml puromycin. After incubation, cells were washed with ice-cold PBS and lysed using RIPA lysis buffer. Lysis were subjected to western blotting and probed with anti-puromycin antibody (Kerafast). β-actin was used as loading control.

Polysome profiling
Cells were treated with indicated drugs for 6 hours and then harvested on ice in PBS containing 100μg/ml cyclohexamide. Cells were pelleted and lysed in lysis buffer (20 mM Tris-HCl (pH 7.4), 250 mM NaCl, 15 mM MgCl₂, 0.5% Triton X-100, 1 mM DTT, 100μg/ml cyclohexamide, and Protease inhibitor cocktail, TURBO DNase and RNase). Lysates were passed with 23G needle to homogenize. Lysates were cleared, separated on a 10%–50% sucrose gradient by ultracentrifugation, and fractionated using a Piston Gradient Fractionator (Biocomp). Absorbance at OD260 was measured.

Statistical methods
In vitro quantitative tests such as cell viability experiments were conducted in triplicate, and the mean and standard error was calculated. Unpaired Student's t test was used to compare two independent groups. One-way analysis of variance (ANOVA) was used when three or more independent groups were compared. All tests were two-sided. A P value < 0.05 was considered statistically significant. For the animal experiment, the statistical significance of treatment effectiveness was calculated by the difference between mean tumor volumes in the control and treatment groups for each time point by repeated measure ANOVA. Dunnett's multiple comparison test was used to smooth the significance level for multiple simultaneous hypothesis tests. The statistical significance of body weight was calculated by Unpaired-t-test. Data were analyzed using the Prism 5 program (GraphPad Software) and prism online tools.

SUPPLEMENTAL REFERENCES
1. Deng, C. et al. Silencing c-Myc translation as a therapeutic strategy through targeting PI3Kδ and CK1ε in hematological malignancies. Blood 129, 88–99 (2017).
SUPPLEMENTAL FIGURE LEGENDS

Figure S1. A dual CK1ε/CK1δ inhibitor PF670462 reduces phosphorylation of 4E-BP1 in Z-138 lymphoma cells

(A) Immunoblotting assay. The indicated lymphoma cell lines were treated with PF670462 at the indicated concentrations or vehicle control for 6 h and 24 h. Protein levels were determined by immunoblot. ‘P-’ before a protein name indicates phosphorylated protein.

Figure S2. SR-3029 is well tolerated and does not affect β-catenin nuclear import in lymphoma.

(A) SR-3029 treatment does not affect mouse body weight. The mean weight of the mice receiving the indicated treatments were plotted against the time of treatment. We observed no statistically significant differences among the cohorts of 8 mice as determined by unpaired student’s t-test: (i) vehicle control group, which received vehicle of 10% DMSO, 10% Tween-20, and 80% water; (ii) SR-3029 at 30 mg/kg daily and (iii) SR-3029 at 40 mg/kg daily.

(B, C) SR-3029 does not affect β-catenin nuclear import in lymphoma cells. lymphoma cell lines Z-138 (B) and OCI-LY10 (C) were treated with SR-3029 or DMSO control for 24 h as indicated. Nuclear and cytoplasmic fractions were isolated and assayed for the level of β-catenin by immunoblot. Tubulin and Lamin B1/Histone were used as loading controls for cytoplasmic and nuclear proteins, respectively.

(D) Response of PBMCs from healthy donors # 1-4 to SR-3029 treatment for 48 h was determined with the Cell Titer Glo assay.

(E) Protein levels of CK1δ in lymphoma cell lines and peripheral blood mononuclear cells (PBMCs) from healthy donors were determined with immunoblotting.

SUPPLEMENTAL TABLE LEGENDS

Table S1. IC50 and IC90 values were calculated for SR-3029 at 24 and 48 h as determined by the Cell Titer Glo assay.
Figure S1

Z-138

| PF670462 (µM) | 6 h | 24 h |
|---------------|-----|------|
|                | 0   | 0    |
| P-4E-BP1       | 0   | 0    |
| S65            | 0   | 0    |
| 4E-BP1         | 0   | 0    |
| β-actin        | 0   | 0    |
Table S1. IC\textsubscript{50} and IC\textsubscript{90} values of SR-3029.

| Cell line     | 24h       | 48h       |
|---------------|-----------|-----------|
|               | SR-3029 IC\textsubscript{50} (nM) | SR-3029 IC\textsubscript{90} (nM) | SR-3029 IC\textsubscript{50} (nM) | SR-3029 IC\textsubscript{90} (nM) |
| Jeko-1        | 822.8     | 1397.4    | 202.3     | 253.1     |
| Z-138         | 212.5     | 366       | 168.1     | 343       |
| Maver-1       | 500       | 3958      | 139       | 338       |
| JVM-2         | 107.9     | 823.7     | 22.3      | 121.72    |
| OCI-LY7       | 199.8     | 349.6     | 104.2     | 190.6     |
| OCI-LY10      | 81.01     | 155       | 68.5      | 105.4     |
| SUDHL-6       | 103.2     | 128       | 112.3     | 236.7     |
| VAL           | 898.8     | 4164      | ~ 400     | 5148      |
| FEPD          | 404.4     | 674.9     | 324       | 483       |
| SMZ1          | 233       | 531       | 124.8     | 294.3     |
| MAC2A         | 132.2     | 2427      | 75.6      | 222.2     |
| MTA           | 838.9     | ~3570     | 138.1     | 337.3     |
| H929          | 203.5     | 474.4     | 133.5     | 277.2     |
| MM1S          | 203.6     | 665.1     | 81.8      | 264       |
| MCL donor 1   | 258.8     | 683.6     | 136.8     | 343.4     |
| MCL donor 2   | 323.7     | 685.5     | 86.4      | ~3945     |
| MCL donor 3   | > 500     | Ambiguous | 258.4     | ~3762     |
| Healthy don 1 | >500      | Ambiguous | 201.1     | 480       |
| Healthy don 2 | 305       | 5101      | 220.6     | 725       |
| Healthy don 3 | >500      | Ambiguous | 350.2     | 5376      |
| Healthy don 4 | >500      | Ambiguous | 215.3     | ~366      |