Supplementary Figure 1. LCL-161 synergizes with etoposide and vincristine in RRCL models. a) CI values for LCL-161 and vincristine show mostly additive (CI=1) or antagonistic (CI>1) interactions in the Raji cell line. b) Stronger synergy in the Raji 4RH cell line. c) Antagonism was observed between LCL-161 and etoposide in the Raji cell line at all concentrations tested; d) however, synergy was observed between etoposide and LCL-161 in the Raji 4RH cell line, suggesting combinations of LCL-161 and etoposide are more active in RRCLs.

Supplementary Figure 2. LCL-161 does not increase rituximab activity *in vivo*. Animals were inoculated with $1x10^6$ Raji cells or $10x10^6$ Raji 4RH cells. Treatment was administered 7 days after xenograft implantation. Treatment groups were rituximab alone (10mg/kg IV), LCL-161 alone (60mg/kg orally), or a combination of LCL-161 and rituximab given according to the above listed doses and routes of administration. LCL-161 and rituximab were given on day 7. No statistically significant difference in survival was observed between the LCL-161 and LCL-161 + rituximab treatment arms in either cell line model.

Supplementary Figure 3. LCL-161 does not increase carfilzomib activity *in vivo*. Animals were inoculated with $10x10^6$ Raji 4RH cells. Treatment was administered 7 days after xenograft implantation. Treatment groups were LCL-161 alone (60mg/kg orally), carfilzomib alone (2mg/kg IV), or a combination of LCL-161 and carfilzomib given according to the above listed doses and routes of administration. LCL-161 was given on day 7, while carfilzomib was given on days 7 and 8. No treatment arms were statistically distinct from any other treatment arms.

Supplementary Figure 4. Statistical significance values and patient demographics for all samples in the LCL-161 *ex* vivo studies. a) A statistical comparison of anti-tumor responses in *ex vivo* patient samples. P values are for the comparison of 5nM carfilzomib to 5nM carfilzomib + 10uM LCL-161. b) Descriptive statistics of the patient population that *ex vivo* samples were collected from.

Figure S1

a.

Raji LCL-161 + Vincristine (Vin) CI values

	Vin 0.1nM	Vin 0.5nM	Vin 1nM
LCL161 10uM	1.841	5.908	1.214
LCL161 25uM	3.076	0.997	1.061
LCL161 35uM	0.564	0.979	0.967

b.

Raji 4RH LCL-161 + Vincristine (Vin) CI values

	Vin 0.1nM	Vin 0.5nM	Vin 1nM
LCL161 10uM	5.512	0.878	0.815
LCL161 25uM	0.749	0.399	0.385
LCL161 35uM	0.498	0.576	0.432

c.

Raji LCL-161 + Etoposide (Eto) CI values

	Eto 1uM	Eto 2.5uM	Eto 5uM
LCL161 10uM	5.69	2.24	1.944
LCL161 25uM	2.44	3.009	2.895
LCL161 35uM	1.465	1.766	1.755

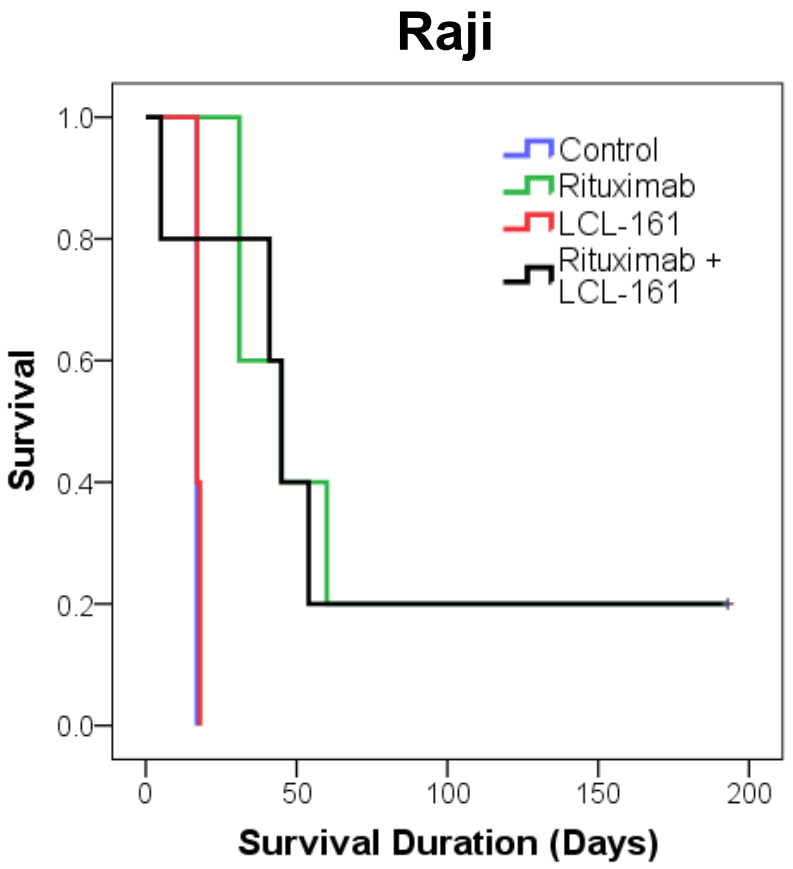
d.

Raji 4RH LCL-161 + Etoposide (Eto) CI values

	Eto 1uM	Eto 2.5uM	Eto 5uM
LCL161 10uM	>10	>10	1.172
LCL161 25uM	1.071	1.48	0.326
LCL161 35uM	1.971	0.551	0.232

CI > 1 (Antagonistic)
CI 0.9 – 0.7 (Slight Synergy)
CI > 0.7 – 0.3 (Moderate Synergy)
CI 0.3 – 0.1 (Synergy)
CI < 0.1 (Strong Synergy)

Figure S2


Raji
Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
Survival Duration (Days)
Control
Rituximab
LCL-161
Rituximab + LCL-161

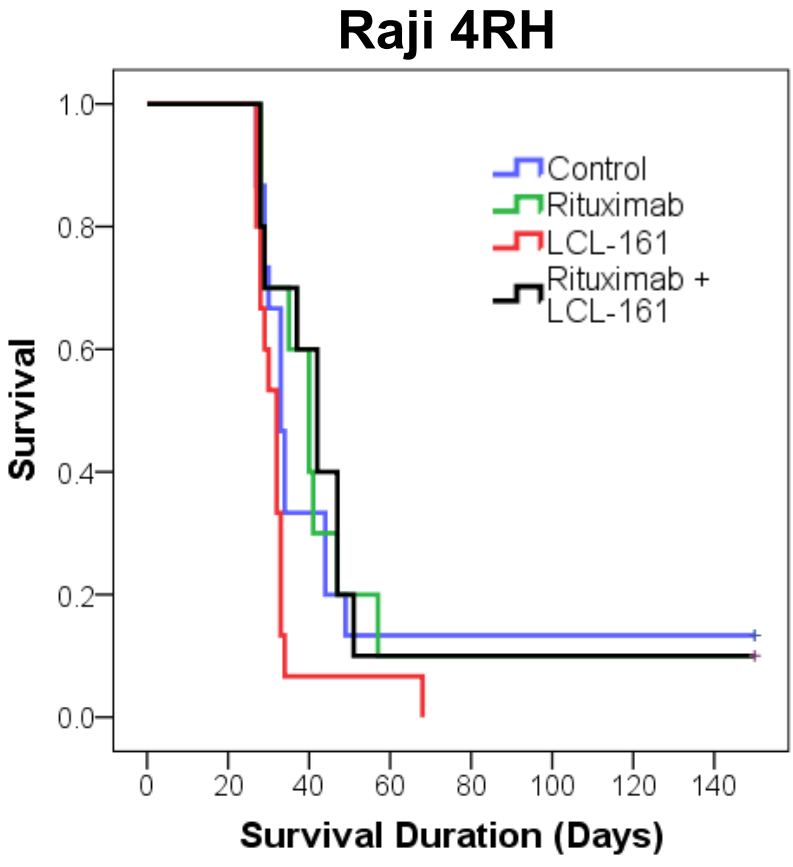

Raji 4RH
Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
Survival Duration (Days)
Control
Rituximab
LCL-161
Rituximab + LCL-161

Figure S3

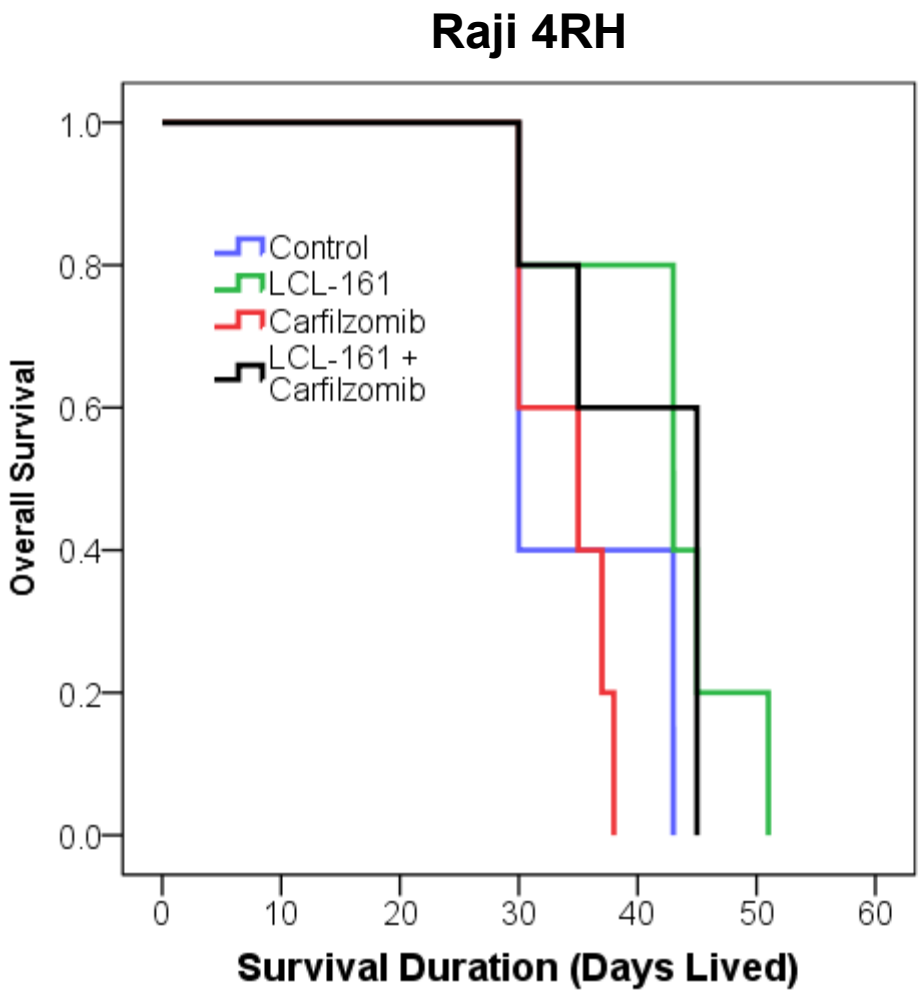

Raji 4RH
Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
Control
LCL-161
Carfilzomib
LCL-161 +
Carfilzomib
0
10
20
30
40
50
60
Survival Duration (Days Lived)

Figure S4

a.

Patient Number	Diagnosis	Biopsy Site	Age and Gender	Prior Therapy	Lifetime Rituximab (mg/m^2)
141	ABC-DLBCL	Lung	20, M	R-EPOCH, R-ICE, R-DHAC, HyperCVAD	3750
121	FL, grade IIIA	Tonsil	73, M	None	0
109	FL, grade IIIA	Lymph node	71, M	R-CHOP, R-Bendamustine	4500
123	FL, grade I-II	Lymph node	79, F	None	0
127	FL, grade not availa-ble	Lymph node	77, F	R-fludarabine, R-doxil	4500
130	FL, grade not availa-ble	Lymph node	69, F	R-CHOP, R-fludarabine	3375
139	MZL	Spleen	67, F	None	0
164	MZL	Spleen	69, M	None	0
110	MZL	Spleen	51, F	R-fludarabine	2250
160	MZL	Spleen	66, M	Steroids	0
128	MCL	Lymph node	66, M	None	0
137	MCL	Blood	62, M	None	0
138	MCL	Bone mar-row	51, M	None	0
165	MCL	Lymph node	39, M	None	0
146	MCL	Blood	M, 56	R-hyperCVAD, HDC-ASCT, BTZ, Ibrutinib	2250

b.

Number of Cases	15
Median age, years (Range)	61 (20-79)
Sex: M/F	10/5
Disease Status •De Novo/Relpase	7/8

ABC-DLBCL: Activated B-cell diffuse large B-cell lymphoma, FL: Follicular lymphoma, MZL: Marginal zone lymphoma, MCL: Mantle cell lymphoma, R-EPOCH: Rituximab, Etoposide phosphate, Prednisone, Vincristine sulfate, Cyclophosphamide, and Doxorubicin hydrochloride, R-ICE: Rituximab, Ifosfamide, Carboplatin and Etoposide, R-DHAC: Rituximab, Dexamethasone and high-dose Cytarabine, HyperCVAD: Cyclophosphamide, Vincristine, Doxorubicin and Dexamethasone, HDC-ASCT: high-dose chemotherapy and autologous stem cell transplantation, BTZ: Bortezomib, M: Male, F: Female