**Supplementary Information**

**Contents:**

**Reagents and antibodies**

Reagents

| | |
|---|---|
| Venor® GeM OneStep kit | Minerva Biolabs, Berlin, Germany |
| AllPrep DNA/RNA Mini Kit | Qiagen, Hilden, Germany |
| RNA 6000 Nano Kit | Agilent Technologies, Santa Clara, CA, USA |
| TruSeq Stranded mRNA Library Preparation Kit | Illumina, San Diego, CA, USA |
| OptiPrep™ | Serumwerk Bernburg, Bernburg, Germany |
| Ficoll® Paque Plus | Cytiva, Marlborough, MA, USA |
| RPMI 1640 | Thermo Fisher Scientific, Waltham, MA, USA |
| L-Glutamine | PAN-Biotech, Aidenbach, Germany |
| Penicillin-streptomycin | PAN-Biotech |
| 100x MEM NEAA | PAN-Biotech |
| Propidium iodide | Sigma-Aldrich, St. Louis, MO, USA |

Reagents - inhibitors

| | |
|---|---|
| Ibrutinib | Selleck Chemicals, Absource Diagnostics, Munich, Germany |
| IACS-010759 | Selleck Chemicals |

Antibodies – cytotoxicity assays

| | |
|---|---|
| CD52 mAb (#MA5-16999) | Invitrogen, Thermo Fisher Scientific |
| Rat IgG2bκ Isotype Control (#16-4031-81) | eBioscience™, Thermo Fisher Scientific |

Antibodies – western blots

| | |
|---|---|
| PARP (#9532) | Cell Signaling Technologies, Danvers, MA, USA |
| p-BTK (#5082) | Cell Signaling Technologies |
| BTK (#3533) | Cell Signaling Technologies |
| β-Actin (#4970) | Cell Signaling Technologies |
| Anti-rabbit IgG, HRP-linked Antibody (#7074) | Cell Signaling Technologies |

Antibodies – flow cytometry

| | |
|---|---|
| CD19-FITC (#FAB4867F) | R&D Systems, Minneapolis, MN, USA |
| C3b/iC3b-FITC (#846108) | BioLegend, San Diego, CA, USA |
| Mouse IgG1κ (#IC002F) | R&D Systems |
| CD52-PE (#130-123-972) | Miltenyi Biotech, Bergisch Gladbach, Germany |
| REA Control (S) PE (#130-113-438) | Miltenyi Biotech |
| CD52-APC (#130-099-632) | Miltenyi Biotech |
| REA Control (S) APC (#130-113-434) | Miltenyi Biotech |

**Supplementary Table 1:** Enriched KEGG pathways of 4 d ibrutinib-treated REC-1

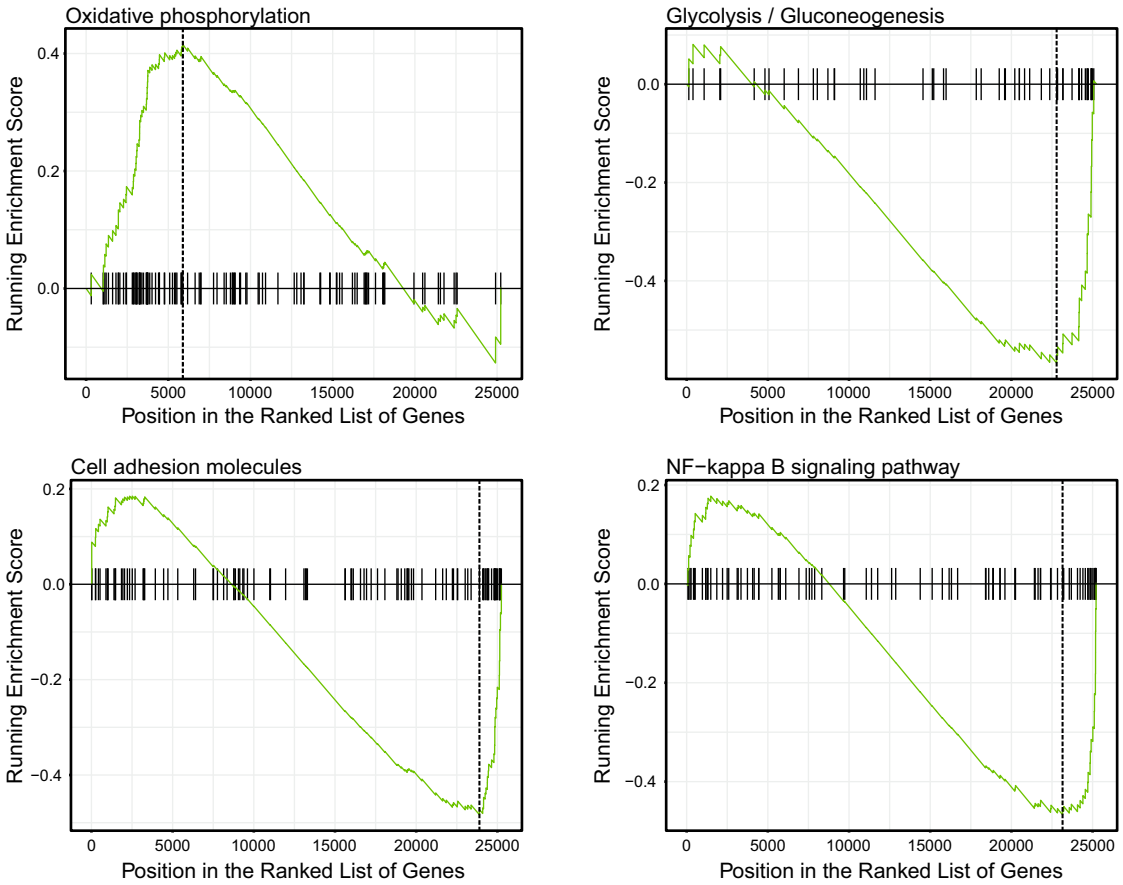
For gene sets with |log2FC| ≥ 1 and q value < 0.05 of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway gene set enrichment analysis (GSEA) of 4 d ibrutinib treated REC-1 (versus untreated) see excel file of Supplementary Table 1.

**Supplementary Table 2:** Characteristics of primary samples

| Sample | Type | Sex | Mantle cell lymphoma subtype | Therapy prior to sample collection | In vitro (treatment) |
|---|---|---|---|---|---|
| P1 | PBMC | m | classic nodal | no | 3 d |
| P2 | PBMC | m | classic nodal | no | 3 d |
| P3 | PBMC | m | classic nodal | yes, Nordic protocol, ibrutinib | 2 d |
| P4 | PBMC | m | classic nodal | no | 2 d |
| P5 | PBMC | f | leukaemic non-nodal | no | 3 d |
| P6 | PBMC | m | classic nodal | no | 3 d |
| P7 | PBMC | m | classic nodal | no | 3 d |
| P8 | PBMC | m | classic nodal | no | 3 d |
| L1 | Lymph node | m | classic nodal | n.a., pre-ibrutinib era | 2 d |
| L2 | Lymph node | m | classic nodal | n.a., pre-ibrutinib era | 2 d |
| H1 | PBMC | f | healthy control | no | 2 d |
| H2 | PBMC | f | healthy control | no | 3 d |

PBMC = peripheral blood mononuclear cells, m = male, f = female, d = days

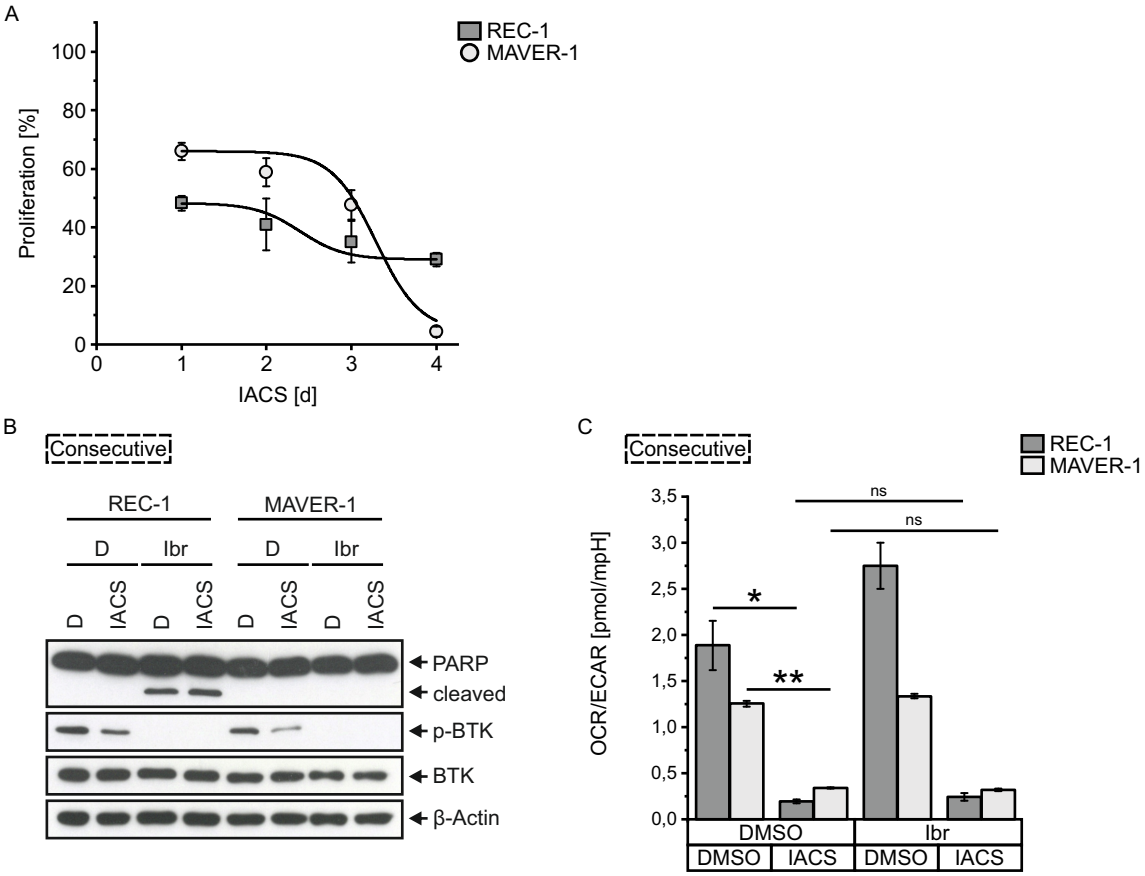
**Supplementary Figure 1**




Supplementary Figure 1: Enrichment plots for selected KEGG pathways of 4 d ibrutinib-treated REC-1.

Enrichments plots of selected significant gene sets by the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway gene set enrichment analysis (GSEA) of 4 d ibrutinib treated REC-1 compared with untreated ($|\log2FC| \geq 1$, q value $< 0.05$).

**Supplementary Figure 2**




Supplementary Figure 2: IACS-010759 kinetics and consecutive treatment with ibrutinib and IACS-010759.

A) Proliferation of REC-1 and MAVER-1 across 1 to 4 d treatment with 25 nM IACS-010759, determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay (N = 3). B) Western blot with PARP, p-BTK, BTK, and β-Actin as loading control (representative for N = 3), after consecutive treatment with 3 d ibrutinib pretreatment (400 nM, DMSO as control) followed by isolation and incubation of viable cells with 25 nM IACS-010759 or DMSO and 400 nM ibrutinib or DMSO according to pretreatment for 2 more days. C) Extracellular Flux analysis showing oxygen consumption rate (OCR) vs extracellular acidification rate (ECAR) ratios of REC-1 and MAVER-1 after consecutive treatment with 3 d ibrutinib pretreatment (400 nM, DMSO as control) followed by incubation with 25 nM IACS-010759 or DMSO and 400 nM ibrutinib or DMSO according to pretreatment for 2 more days (N = 4) .

Data is shown as mean ± SEM. Significance was determined by Student's t-test or a Welch's t-test, for equal or unequal variances, respectively. * $P < 0.05$, ** $P < 0.01$, $P > 0.05$ not significant (ns).