Supplemental Legends

Supplemental Figure 1. Time to event efficacy endpoints.

Supplemental Figure 2. Comparison of tumor-free NSG mice (NSG) versus NSG mice engrafted with DFTL-78024. A) Phenotype of splenic macrophages based on F4/80 and CD11b expression. B) Spleen weight/total body weight in mice treated with vehicle or Duvelisib. C) Expression of CD206 and MHC-II on F4/80+CD11b+ splenic macrophages from NSG mice treated with vehicle or Duvelisib or mice engrafted with DFTL-78024. D) Flow cytometry and E) Immunoblotting for phosphor-AKT at serine 473 in hCD45+ DFTL-78024 cells isolated from the spleen of mice treated with vehicle (V) or Duvelisib (n=3 mice per condition). The pAKT-expressing cell line OCI-LY13.2 is shown for comparison. F) Flow cytometry for annexin V and 7-AAD in hCD45+ DFTL-78024 cells isolated from the spleen of mice treated with vehicle or Duvelisib (two-way ANOVA with Bonferroni correction: p=NS).

Supplementary Methods

Cells, antibodies and small molecules

DERL2[1] cells were obtained from DSMZ, Karpas-384[2] cells from Sigma-Aldrich, DL-40[3], MTA[4] and KHYG-1[5] cells from JCRB. FEPD[6], MAC2A[7], OCI-Ly13.2[8] and OCI-Ly12[8] were kindly provided by Leandro Cerchietti (Weill Cornell Medicine, New York, USA), NKL[9] cells by Jerome Ritz (Dana-Farber Cancer Institute, Boston, USA) and SMZ1[10] cells by Hitoshi Ohno (Tenri Medical Institute, Tenri, Japan). Cells were cultured according to the vendor's recommendation. Cell lines were routinely tested for Mycoplasma (ATCC® Universal Mycoplasma Detection Kit) and authenticity was validated by short tandem repeat (STR)-profiling. Antibodies for Akt (C67E7), Phopsho-Akt (Ser473) (D9E), PI3 kinase p110α (C73F8), PI3 kinase p110γ (D55D5), Caspase-3 (8G10) and α-Tubulin (11H10) were purchased from Cell Signaling Technology. PI3 kinase p110δ (H-219) polyclonal antibody was purchased from Santa Cruz. Duvelisib (IPI-145), BKM-120 and A-66 were purchased from Selleckchem.

In vitro analyses and statistics

Dose-response curves were generated with GraphPad Prism software. Continuous variables were compared with 2-sided Student t tests and categorical variables with 2-sided Fisher's exact tests. The phosphoproteomic signature of OCI-Ly13.2, DERL2 and Karpas384 were defined as sensitive, the signature of MAC2A, OCI-Ly12 and SMZ1 as resistant and all pairwise differences between the profiles in the categories were computed. These differences were randomly resampled into groups of 9 (the original number of sensitive and resistant samples) 100 times to generate representative differential phosphorylation profiles. These phosphoprofiles were compared against a collection of existing P100 phosphoprofiles (https://panoramaweb.org/labkey/lincs.url) that contains the phosphoproteomic signature of a library of drugs to obtain quantitative *connectivity* profiles, which were then collapsed across all 100 iterations by their medians. The drug profiles in the library are grouped by the mechanism of action (MoA) of the drug, with each group being classified as a perturbation set corresponding to

a particular MoA. The resulting median connectivity profile was used to perform an enrichment analysis against the pre-defined perturbation sets as previously described (unweighted ssGSEA).[11]

GR50 and GRmax values were calculated, using the GR calculator at www.grcalculator.org, as previously described [12]. Drug synergy was calculated using the chalice synergy calculator at http://chalice.horizondiscovery.com/analyzer-server/cwr/analyze.jsp. Heatmap were generated with Morpheus at https://software.broadinstitute.org/morpheus.

Endpoints, analyses, and statistics

All patients who received any dose of Duvelisib were included in the analyses. Patients with PTCL were assessed for disease response or progression by the investigator with computed tomography (CT) scans and fluorodeoxyglucose-positron emission tomography (FDG-PET), where indicated, using International Working Group (IWG) Response Criteria.[13] For CTCL patients, skin responses were derived using the modified severity weighted assessment tool (mSWAT).[14] Response assessments were performed on or just prior to day 1 of cycles 3, 5, 7, 10, 13, 16, and 19, and every sixth cycle thereafter until treatment discontinuation. A bone marrow biopsy and/or aspiration (PTCL subjects only) was performed only to confirm a radiographic complete response. Efficacy was assessed by evaluating overall response rate (ORR), defined as the best overall response (OR) of complete response (CR) or partial response (PR); best OR, defined as the best response (based on investigator assessment) achieved by a subject during the study; time to response (TTR), defined as the time from the first dose of study drug to the first documentation of response; duration of response (DOR), defined as time from the first documentation of response to first documentation of progressive disease (PD) or death due to any cause; progression-free survival (PFS), defined as time from first dose to either PD or death; and overall survival (OS), defined as time from first dose of study drug to death. Measurements of safety by adverse event (AE) and clinical laboratory assessment were conducted at all clinic visits. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

Serum collected from 19 consenting patients at Baseline and Cycle 1-Day 8 was analyzed for evidence of pharmacodynamics modulation. Serum proteins were analyzed from samples using Luminex® xMAP technology, wherein analytes were captured on uniquely labeled fluorescent beads, and the amount of analyte was quantified using a specialized camera. Multiplex panels of cytokines, chemokines, and matrix metalloproteinases (MMPs) covering 72 analytes were evaluated. Each sample was tested in duplicate, and duplicate measurements were averaged.

Descriptive statistics, including median and range or mean and coefficient of variation for continuous endpoints and frequency and percentage for categorical endpoints, are presented. Analyses of pharmacodynamic data included two-sample t-test comparisons of Cycle 1-Day 1 values compared to values from samples from healthy donors (serum purchased from BioreclamationIVT, Hicksville, NY). The percentile change of serum cytokine levels on Cycle 1-Day8 compared to baseline was compared between responders (PR/CR) and non-responders (PD) with a Mann-Whitney test. For the ORR, the Clopper-Pearson 95% confidence interval (CI) is provided. PFS and OS are summarized using Kaplan-Meier methods.

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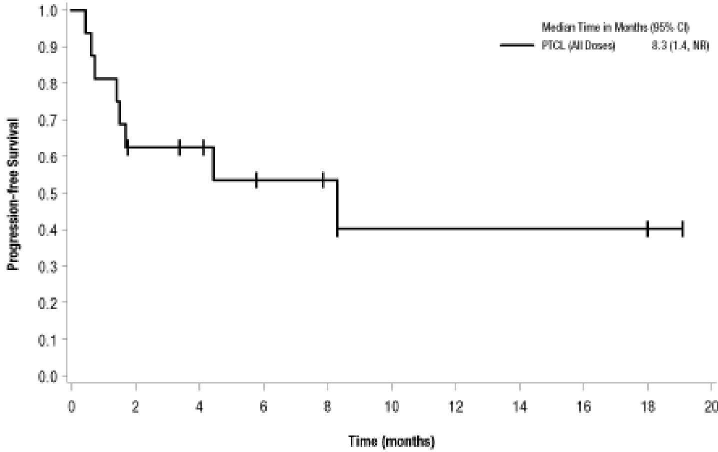
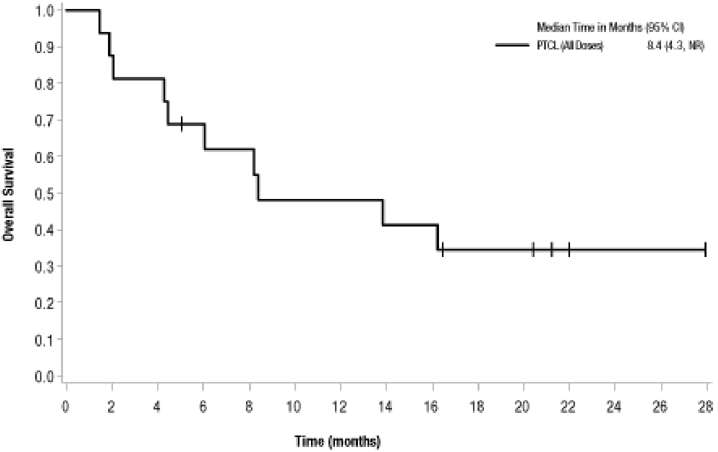
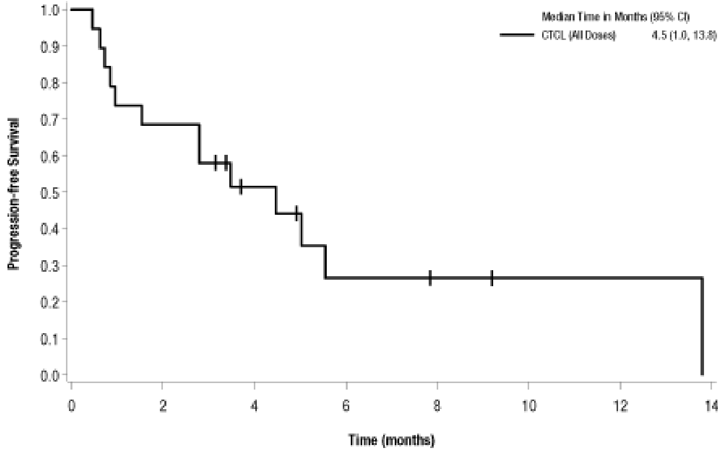
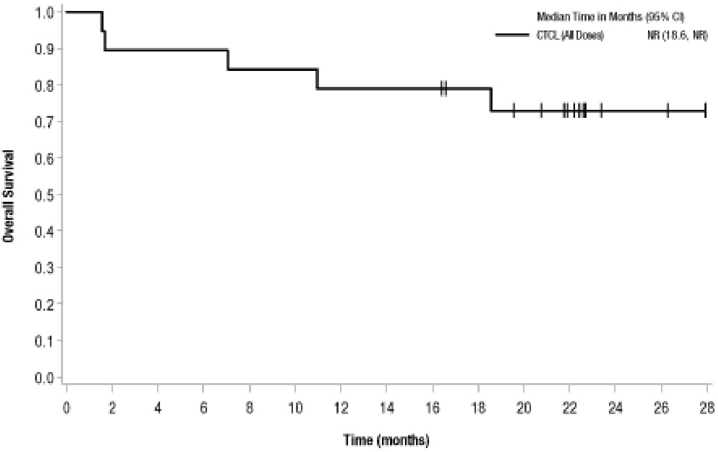
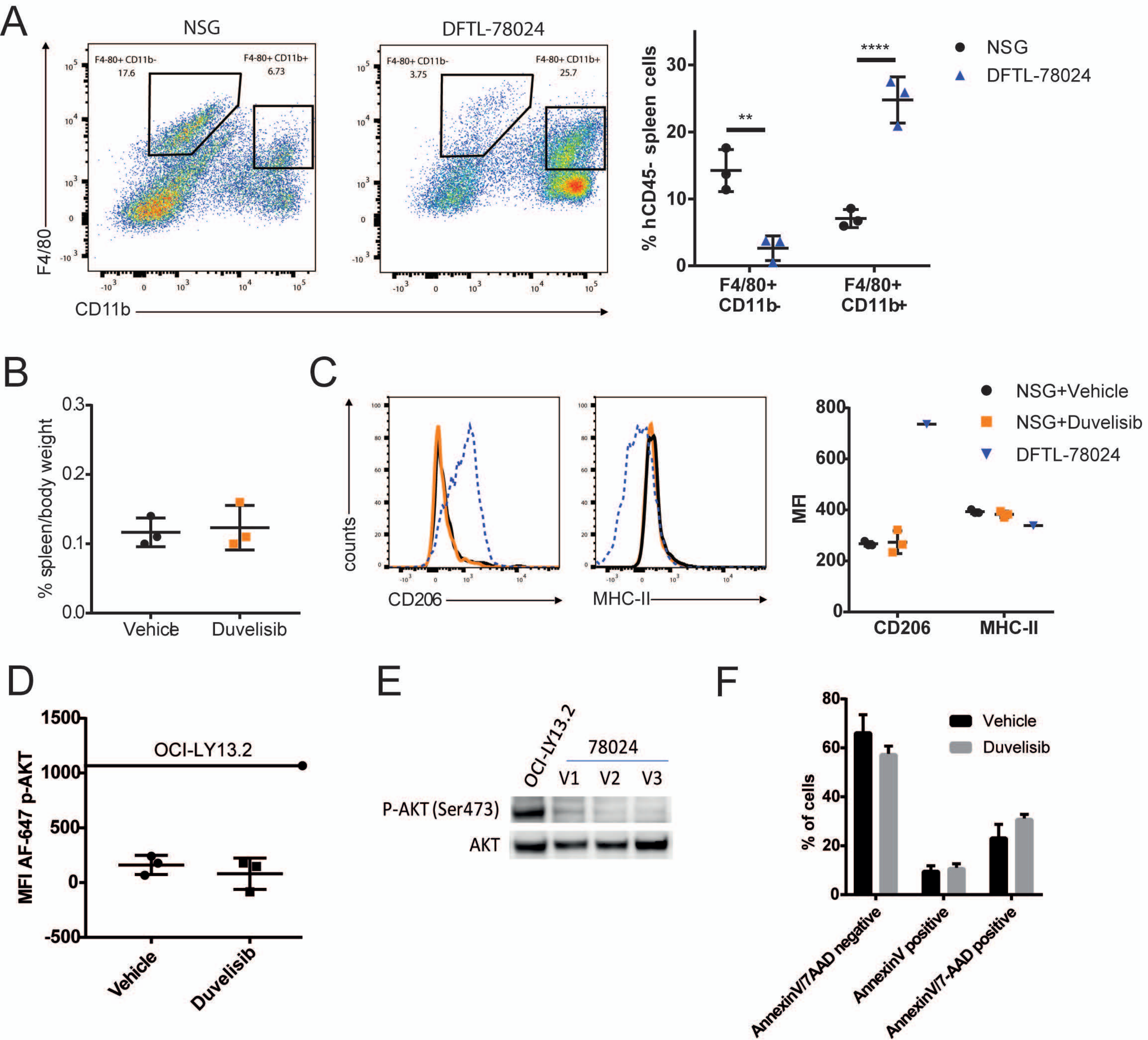
Supplemental Figure 1. Time to event efficacy endpoints.











Supplementary Figure 2