Temsirolimus combined with cyclophosphamide and etoposide for pediatric patients with relapsed/refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium trial (TACL 2014-001)

Sarah K. Tasian,[1,2] Lewis B. Silverman,[3] James A. Whitlock,[4] Richard Sposto,[5] Joseph P. Loftus,[1] Eric S. Schafer,[6] Kirk R. Schultz,[7] Raymond J. Hutchinson,[8] Paul S. Gaynon,[9] Etan Orgel,[9] Caroline M. Bateman,[10] Todd M. Cooper,[11] Theodore W. Laetsch,[1,2] Maria Luisa Sulis,[12] Yueh-Yun Chi,[9] Jemily Malvar,[9] Alan S. Wayne[9] and Susan R. Rheingold[1,2]

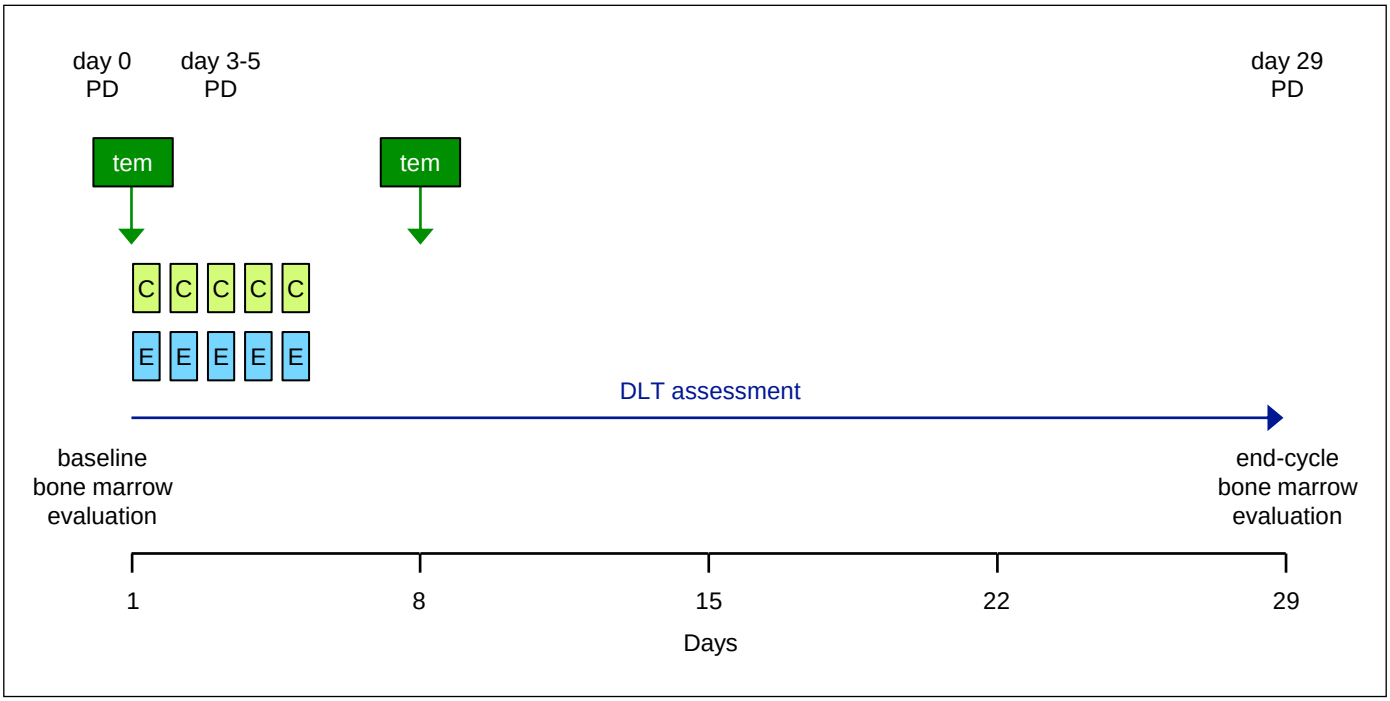
[1]Division of Oncology and Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [3]Department of Pediatric Oncology, Dana-Farber Cancer Institute and Division of Pediatric Hematology-Oncology, Boston Children's Hospital, Boston, MA, USA; [4]Division of Haematology/Oncology, Hospital for Sick Children and the University of Toronto, Toronto, Ontario, Canada; [5]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [6]Dan L. Duncan Institute for Clinical and Translational Research, Baylor College of Medicine and Texas Children's Cancer Center, Houston, TX, USA; [7]Division of Hematology/Oncology/Bone Marrow Transplant, British Columbia Children's Hospital, Vancouver, British Columbia, Canada; [8]Division of Hematology/Oncology, CS Mott Children's Hospital, Ann Arbor, MI, USA; [9]Division of Hematology/Oncology, Children's Hospital Los Angeles, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [10]Cancer Centre for Children, The Children's Hospital at Westmead, Westmead, New South Wales, Australia; [11]Division of Hematology/Oncology, Seattle Children's Hospital Cancer and Blood Disorders Center, Seattle, WA, USA and [12]Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Correspondence: S. R. Rheingold
rheingold@chop.edu

Received: June 25, 2021.
Accepted: December 7, 2021.
Prepublished: February 3, 2022.

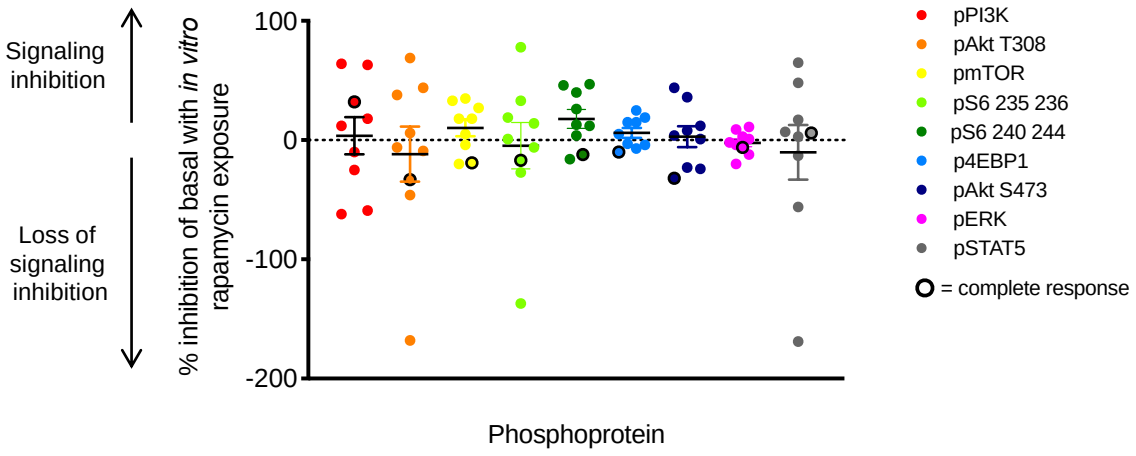
https://doi.org/10.3324/haematol.2021.279520

Supplemental Figure 1



Schema of clinical trial drug dosing and patient specimen sampling schedule. Pediatric patients with relapsed/refractory ALL enrolled on the TACL2014-001 phase 1 clinical trial underwent baseline bone marrow aspiration/biopsy at study entry to determine level of bone marrow involvement. Consenting patients also provided peripheral blood specimens pre-treatment (day 0) and post-treatment (days 3-5 and day 29) for pharmacodynamic (PD) assays of *in vivo* signaling inhibition by single-cell phosphoflow cytometry analyses. Patients were treated with cyclophosphamide (C) 440 mg/m^2 and etoposide (E) 100 mg/m^2 daily IV on days 1-5 and with temsirolimus IV on days 1 and 8 at the cohort-specified dosing. Patients were assessed for dose-limiting toxicity (DLT) of the temsirolimus/cyclophosphamide/etoposide regimen through day 29 of cycle 1 and underwent repeat bone marrow aspiration/biopsy at end-cycle 1. Patients with at least partial response to the treatment regimen were permitted to receive a second cycle of therapy.

Supplemental Figure 2



Summary data of temsirolimus-induced phosphosignaling inhibition in treated patients. Pre-treatment (basal) and post-treatment levels of PI3K/mTOR pathway phosphoproteins were measured as median fluorescence intensity (MFI) by single-cell phosphoflow cytometry in gated B-ALL or T-ALL cells in peripheral blood specimens from TACL 2014-001 patients. Phosphoprotein inhibition in peripheral blood ALL cells at Day 3-5 of therapy after the first dose of temsirolimus in comparison to basal phosphoprotein levels is shown for each patient treated at all dose levels (DL1, DL2, DL3, DL4) in this comprehensive summary display of individual dose level data shown in Figure 1. MFI data were normalized intra-patient to pre-treatment levels of each phosphoprotein. Central horizontal lines depict mean phosphoprotein inhibition for inter-patient comparison. Solid symbols = patients with stable or progressive disease after cycle 1, black-ringed symbols = complete response.