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Resumo	Purpose: Despite the remarkable activity of BTK inhibitors (BTKi) in relapsed B-cell non-Hodgkin lymphoma (B-NHL), no clinically-relevant biomarker has been associated to these agents so far. The relevance of phosphoproteomic profiling for the early identification of BTKi responders remains underexplored. Experimental design: A set of six clinical samples from an ongoing phase I trial dosing patients with chronic lymphocytic leukemia (CLL) with TG-1701, a novel irreversible and highly specific BTKi, were characterized by phosphoproteomic and RNA sequencing (RNA-seq) analysis. The activity of TG-1701 was evaluated in a panel of 11 B-NHL cell lines and mouse xenografts, including two NF-κB- and BTKC481S-driven BTKi-resistant models. Biomarker validation and signal transduction analysis were conducted through real-time PCR, Western blot analysis, immunostaining, and gene knockout (KO) experiments. Results: A nonsupervised, phosphoproteomic-based clustering did match the early clinical outcomes of patients with CLL and separated a group of "early-responders" from a group of "late-responders." This clustering was based on a selected list of 96 phosphosites with Ikaros-pSer442/445 as a potential biomarker for TG-1701 efficacy. TG-1701 treatment was further shown to blunt Ikaros gene signature, including YES1 and MYC, in early-responder patients as well as in BTKi-sensitive B-NHL cell lines and

	xenografts. In contrast, Ikaros nuclear activity and signaling remained unaffected by the drug in vitro and in vivo in late-responder patients and in BTKC481S, BTKKO, and noncanonical NF-κB models. Conclusions: These data validate phosphoproteomic as a valuable tool for the early detection of response to BTK inhibition in the clinic, and for the determination of drug mechanism of action.
Fomento	