Mounting evidence implicates the tumor microenvironment in maintenance and expansion of leukemia, suggesting interplay between cell-autonomous lesions and external factors in disease progression. The cytokine interleukin-7 (IL-7) has been implicated in leukemogenesis in vivo, since IL-7 transgenic mice develop lymphoid malignancies. We showed that IL-7 induces proliferation and viability of T-ALL cells by downregulating p27kip1, leading to cell cycle progression and Bcl-2 upregulation. These effects are dependent on phosphoinositide-3-kinase (PI3K), which is also critical for IL-7-mediated T-ALL cell growth, glucose uptake, and Glut1 upregulation. Hence, PI3K appears to be a key regulator of T-ALL cell metabolism. Interestingly, several T-ALL cell lines have high basal activation of PI3K-Akt pathway due to lack of PTEN, a phosphatase that counteracts PI3K activity. However, it is not clear whether the same occurs in primary disease. We thus evaluated the integrity of PTEN-PI3K-Akt axis in T-ALL samples at diagnosis. Hyperactivation of PI3K-Akt pathway occurs in all T-ALL samples analyzed and is critical for T-ALL viability, since the PI3K inhibitor LY294002 compromises mitochondrial membrane integrity, upregulates FasL and specifically induces atrophy and apoptosis of primary T-ALL cells, while not affecting normal T-cell precursors. Further studies revealed that whereas primary T-ALLs express PTEN mRNA, 24% of the cases analyzed lack PTEN protein. Interestingly, all PTEN protein-null samples show PTEN gene alterations, mainly in exons 1 and 7. In contrast, PTEN protein-positive T-ALLs do not have PTEN mutations and, surprisingly, express even higher PTEN protein levels than normal controls. We show that constitutive activation of PI3K-Akt pathway in primary T-ALL cells occurs not only via the canonical mechanism involving PTEN gene lesions leading to protein deletion, but also through a mechanism not previously described in T-ALL that involves PTEN phosphorylation, stabilization and inactivation. Hence, constitutive activation of PI3K-Akt pathway in T-ALL is not exclusive to established cell lines and may be critical for the onset/progression of this malignancy. Importantly, our data suggest that PI3K inhibitors are promising tools for the development of novel therapeutic strategies in human T-cell leukemia.