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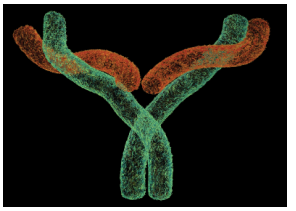
Clinical Trials

Major finding: KW-0761 monotherapy achieved a 50% response rate in patients with relapsed ATL.

Approach: A multicenter, single-arm phase II trial evaluated the efficacy of weekly KW-0761 infusion.

Impact: Patients with CCR4-positive T-cell neoplasms may benefit from KW-0761 treatment.

AN ANTI-CCR4 ANTIBODY ELICITS AN ANTITUMOR RESPONSE IN ATL PATIENTS



Adult T-cell leukemia–lymphoma (ATL), a highly aggressive peripheral T-cell malignancy caused by human T-cell lymphotropic virus type I, is resistant to conventional chemotherapies and therefore carries a very poor prognosis. The observation that CC chemokine receptor 4 (CCR4) is expressed on ATL tumor cells prompted the development of KW-0761, a next-generation humanized anti-CCR4 monoclonal antibody with a defucosylated Fc region, which enhances antibody-dependent cellular cytotoxicity. Preclinical studies using KW-0761 demonstrated robust antitumor responses, and a phase I clinical trial showed preliminary potent activity against ATL in patients. In a multicenter, single-arm phase II study, Ishida and colleagues investigated the efficacy, pharmacokinetic profile, and safety of KW-0761 monotherapy in patients with relapsed CCR4-positive ATL (acute, lymphoma, or unfavorable chronic type) who had failed one or more prior chemotherapy regimens. The 2 most common treatment-related adverse events, infusion reaction and skin rash, were reportedly tolerable and reversible. For 26 evaluable patients, the overall response rate was 50%, with 8 patients achieving a complete response. The median progression-free survival and overall survival were 5.2 and 13.7 months, respectively, and patients with ATL of the blood had a higher response rate than those with skin or nodal and extranodal ATL. Although this trial was performed in a small, clinically heterogeneous patient population, it nevertheless demonstrates the efficacy and safety of KW-0761 in relapsed ATL patients. Additional studies may elucidate whether KW-0761 will show therapeutic activity against other CCR4-positive T-cell cancers. Furthermore, because KW-0761 treatment resulted in a significant and lasting decrease in endogenous non-ATL regulatory T cells as well as ATL cells, KW-0761 could potentially be used to boost antitumor immunity. ■

Ishida T, Joh T, Uike N, Yamamoto K, Utsunomiya A, Yoshida S, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. J Clin Oncol 2012 Feb 6. [Epub ahead of print].

Drug Resistance

Major finding: *ALK* gene alterations or activation of other RTKs can drive crizotinib resistance.

Clinical relevance: ALK mutants vary in sensitivity to second-generation ALK inhibitors.

Impact: Second-line therapies should be tailored to individual crizotinib resistance mechanisms.

CRIZOTINIB RESISTANCE ARISES THROUGH MULTIPLE MECHANISMS

Patients with non–small cell lung cancer (NSCLC) harboring the *EML4-ALK* fusion oncogene are highly responsive to the ALK tyrosine kinase inhibitor crizotinib but inevitably relapse. Katayama and colleagues and Doebele and colleagues cataloged the mechanisms of acquired drug resistance in biopsies from *EML4-ALK*–positive NSCLC patients who progressed while on crizotinib. In 22% to 36% of patients, sequencing of the ALK kinase domain exons identified multiple mutations resulting in distinct amino-acid substitutions or insertions that are predicted to impair crizotinib binding. Katayama and colleagues found that the different ALK mutants varied in their sensitivity to second-generation ALK inhibitors, with the 1151Tins mutation showing resistance to all ALK inhibitors tested. However, the HSP90 inhibitor 17-AAG potently suppressed the growth of cells harboring any of the ALK kinase mutants *in vitro*. Another 6% to 9% of the crizotinib-resistant patients had acquired high-level amplification of the *EML4-ALK* fusion gene. To characterize the underlying resistance mechanisms in the remaining patients, the teams screened for mutations in a panel of cancer-related genes using a multiplexed genotyping platform and screened for receptor tyrosine activation (RTK) in crizotinib-resistant cells using phospho-RTK arrays. These approaches identified EGFR, KIT, and RAS activation as bypass mechanisms mediating acquired resistance in crizotinib-refractory patients. Notably, some patients appeared to have acquired *ALK* mutations, fusion gene amplifications, and/or RTK-activating genetic lesions simultaneously. Although it is clear that additional means of crizotinib resistance remain to be identified, these findings illustrate the heterogeneity and redundancy of drug resistance mechanisms in *EML4-ALK*–positive NSCLCs and indicate that second-generation ALK inhibitors, HSP90 inhibitors, and combination RTK inhibitor therapy may need to be considered in relapsed patients on a case-by-case basis. ■

Katayama R, Shaw AT, Khan TM, Mino-Kenudson M, Solomon BJ, Halmos B, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. Sci Transl Med 2012;4:120ra17.

Doebele RC, Pilling AB, Aisner DL, Kutateladze TG, Le AT, Weickhardt AJ, et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. Clin Cancer Res 2012 Jan 10. [Epub ahead of print].

AACR American Association for Cancer Research

CANCER DISCOVERY

An Anti-CCR4 Antibody Elicits an Antitumor Response in ATL Patients

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