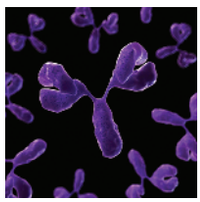
Clinical Trials

Major finding: A first-in-class true human IL1α antibody was well tolerated in patients with metastatic cancer.

Clinical relevance: IL1α neutralization led to a decrease in plasma IL6 levels and increased lean body mass.

Impact: Use of an IL1α blocking antibody may combat pleiotropic effects of inflammation in multiple cancers.

A TRUE HUMAN INTERLEUKIN 1α ANTIBODY IS ACTIVE IN LATE-STAGE CANCERS



Chronic inflammation is a hallmark of cancer and underlies many aspects of the malignant phenotype, such as tumor progression and cachexia. A suitable therapeutic target for reducing cancer-associated inflammation has proven elusive. Interleukin 1α (IL1α) is an early component of inflammatory responses that may promote cancer-associated inflammation through its expression on platelets and leukocytes. Hong and colleagues conducted an open-label, dose-escalation phase I trial to evaluate MABp1, a true human monoclonal antibody specific for IL1α, in 52 adults with refractory metastatic cancers representing 18 different tumor types. The primary objectives were to assess the safety and tolerability of MABp1, characterize its pharmacokinetic profile, and determine the recommended phase II dose. Secondary objectives included evaluation of antitumor activity and pharmacodynamic effects and assessment of changes in cancer-related cachexia and quality of life. MABp1 was very well tolerated, with relatively few adverse effects and no discontinuations due to MABp1 treatment. MABp1 serum concentrations were consistent at all doses. Of 34 evaluable patients, 10 (29%) had stable disease and 1 (3%) experienced a partial response. Serum levels of IL6 were used as a biomarker of IL1α activity; in 42 patients tested, median plasma concentrations of IL6 decreased, though this result was not statistically significant. Of 30 patients evaluated for changes in cancer-associated cachexia, 21 (70%) gained lean body mass; plasma IL6 levels were significantly decreased in these patients but not in those who lost lean body mass. Quality of life significantly improved among 33 patients assessed. Although further testing with a larger number of patients is necessary to determine how the effects of MABp1 are mediated and the effect of IL1α neutralization on survival, these results indicate that targeting IL1α is feasible and provide support for further clinical evaluation of MABp1. ■

Hong DS, Hui D, Bruera E, Janku F, Naing A, Falchook GS, et al. MABp1, a first-in-class true human antibody targeting interleukin-1α in refractory cancers: an open-label, phase 1 dose-escalation and expansion study. Lancet Oncol 2014;15:656–66.

DNA Repair

Major finding: BRCA1 interacts with splicing machinery to regulate DNA damage response gene transcript stability.

Mechanism: BRCA1 Ser1423 phosphorylation regulates pre-mRNA splicing by recruiting BCLAF1 to chromatin.

Impact: Mutation of proteins within the BRCA1-mRNA splicing complex may enhance cancer susceptibility.

BRCA1-MEDIATED mRNA SPLICING MAINTAINS GENOME STABILITY

BRCA1 plays a major role in the DNA damage response and has key functions in DNA repair and transcriptional control. Regulation of BRCA1 is largely driven by ATM- and ATR-mediated phosphorylation; however, the precise roles of specific BRCA1 phosphorylation events remain unclear. Savage and colleagues identified an interaction between BCL2-associated transcription factor 1 (BCLAF1) and BRCA1 phosphoserine-1423 (pSer1423) that was induced by genotoxic stress. Similar to BRCA1 loss, depletion of BCLAF1 sensitized cells to radiation and led to the persistence of unresolved DNA breaks and chromosomal abnormalities, suggesting that BCLAF1 might play a role in BRCA1-mediated DNA damage signaling and repair. Consistent with these findings and with previous work implicating BCLAF1 in pre-mRNA processing, BRCA1 was found to assemble into a multiprotein complex with mRNA splicing proteins in a BCLAF1-dependent manner following DNA damage. BCLAF1 binding to chromatin was largely regulated by BRCA1 pSer1423, suggesting that BRCA1 phosphorylation may regulate gene expression by recruiting BCLAF1 and other mRNA processing machinery to target gene loci. In support of this hypothesis, exogenous DNA damage was shown to stimulate BRCA1-dependent binding of BCLAF1 to the promoters and mRNA transcripts of DNA repair genes and increase the level of mRNA splicing. Suppression of BRCA1 or BCLAF1 led to a reduction in post-spliced transcript levels of *ATRIP*, *BACH1*, and EXO and reduced the stability of these gene transcripts, suggesting that BRCA1-mediated mRNA processing may be required to counteract rapid protein turnover of DNA repair proteins following genotoxic stress. Concomitant overexpression of *ATRIP*, *BACH1*, and *EXO1* was able to partially rescue the radiosensitivity of BRCA1- or BCLAF1-deficient cells, providing further evidence that regulation of these genes by BRCA1 is required for DNA damage resistance and efficient DNA repair. Together, these results uncover a role for BRCA1-mediated regulation of mRNA splicing in the DNA damage response. ■

Savage KI, Gorski JJ, Barros EM, Irwin GW, Manti L, Powell AJ, et al. Identification of a BRCA1-mRNA splicing complex required for efficient DNA repair and maintenance of genomic stability. Mol Cell 2014 Apr 17 [Epub ahead of print].