AFN111, a preclinically safe and effective TCR-engineered T cell therapy targeting the oncogenic driver KRAS G12V mutation

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Abstract
Mutations in the RAS family of genes are responsible for up to 30% of all human cancers. Mutated RAS proteins are crucial oncogenic drivers essential for cancer development and progression making them optimal targets for cancer therapies by limiting tumor escape. The AFN111 T cell therapy consists of autologous CD4+ and CD8+ T cells expressing a TCR specific for the highly prevalent KRAS G12V mutation presented by HLA-A11:01, one of the most common HLA alleles worldwide. AFN111 is also engineered to express the CD3δζ co-constructor, enabling a coordinated CD4+ TCR+ tumor response that aims to promote increased T cell activity and persistence while minimizing T cell exhaustion. Oncolytic T cell therapies, and vaccine-based strategies have been developed targeting several KRAS mutations in multiple tumor cell lines.

AFN111 TCR is activated by endogenously processed and presented KRAS G12V+ 111 peptides across diverse tumor cell lines for in vitro activation, proliferation, and cytotoxicity. In vitro safety studies were performed to define the AFN111 TCR recognition motif and evaluate AFN111 111 T cell peptide cross-reactivity, allogenic activity and cytokine-independent growth. In vivo tumor efficacy studies were conducted using human KRAS G12V+ tumor cell lines in NSG immunocompromised mice after therapeutic administration of AFN111.

Methods
Lentiviral vector was transduced primary human CD4+ and CD8+ T cells with the HLA-A11:01 specific TCR and CD3δζ co-constructor. Engineered T cells were assessed against KRAS G12V+ or KRAS wildtype peptide and a panel of KRAS G12V-expressing tumor cell lines for in vitro activation, proliferation, and cytotoxicity. In vitro safety studies were performed to define the AFN111 TCR recognition motif and evaluate AFN111 111 T cell peptide cross-reactivity, allogenic activity and cytokine-independent growth. In vivo tumor efficacy studies were conducted using human KRAS G12V+ tumor cell lines in NSG immunocompromised mice after therapeutic administration of AFN111.

Summary
AFN111 is a potent and specific TCR-engineered T cell therapy that recognizes KRAS G12V-expressing tumor cell lines both in vitro and in vivo preclinical studies. Cross-reactivity and allogenic activity assessments establish a strong AFN111 preclinical safety profile. AFN111 IND anticipated in 1H’23. First-in-human clinical studies will initiate in collaboration with Fred Hutch Cancer Center. Phase I/II: Safety, tolerability, maximum tolerated dose (MTD), and preliminary efficacy. Clinical Indications: Advanced/metastatic Pancreatic ductal adenocarcinoma (PDAC), Colon adenocarcinoma (CRC), Non-small cell lung cancer (NSCLC). Target population: HLA-A11:01+ KRAS G12V+ patients.

References

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