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Abstract 1217: Preclinical evaluation of a next-generation, EGFR targeting ADC that promotes regression in KRAS or BRAF mutant tumors FREE

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Abstract

Cancers with downstream activating KRAS or BRAF mutations in the EGFR pathway are resistant to EGFR targeting agents such as cetuximab and correspond to a significant unmet need. We hypothesized that an anti-EGFR ADC could be effective against KRAS or BRAF mutated tumors due to the cytotoxic mechanism of the ADC warhead. In an effort to eliminate the known dermal toxicity associated with anti-EGFR therapy, and to mitigate potential toxicities associated with treatment by an anti-EGFR ADC, a mAb was engineered with increased tumor microenvironment (TME) specificity for EGFR. The lead mAb demonstrated undetectable in vivo binding to human donor foreskins grafted onto nude mice, while binding to human A431 tumor xenografts with similar intensity to cetuximab ($P < 0.005$, detected using DyLight-755 conjugated versions of each mAb, measured with a Caliper IVIS system). The lead mAb was further optimized and conjugated to the potent cytotoxic drug MMAE using a novel bis-alkylating conjugation linker, which covalently re-bridged the inter-chain disulfide bonds, creating a stable and defined ADC. The resulting ADC, HTI-1511, incorporated a vc-PAB cleavable moiety and a short linear PEG (24 ethylene glycol units) in a side-chain configuration. Analytical HIC revealed that HTI-1511 possessed a nearly homogenous drug:antibody ratio (DAR) of 4 (>99.7%). Approximately 70% of this compound was rapidly internalized by human tumor cells grown in vitro over 4 hours, overlapping the internalization kinetics of the unconjugated mAb. HTI-1511 was evaluated for efficacy against two human EGFR overexpressing tumor models, MDA-MB-231M (triple-negative breast cancer, KRAS-G13D) and HT-29 (colorectal cancer, BRAF-V600E), and dosed at 5, 10, and 15 mg/kg, (qw, IV). A clear dose dependent anti-tumor response was observed with complete tumor regressions observed at the 15 mg/kg dose in both models, which were resistant to treatment by cetuximab. In addition, HTI-1511 was well-tolerated at 2 and 8 mg/kg in a cynomolgus monkey toxicity study ($n = 3$ per group), with limited dermal findings that were comparable with the vehicle control group. No adverse findings were observed at either dose. HTI-1511 showed a high degree of circulating stability in cynomolgus monkeys, and lacked in vivo degradation and instability that was observed in a control ADC conjugated using maleimide chemistry. HTI-1511 demonstrated significantly attenuated binding to FcγRIIIa, FcγIIb, FcγIIIa 158V, and FcγIIIa 158F receptors, but not attenuated binding to FcγR1, in a FACS based assay format specific for each receptor, suggesting that HTI-1511 might have improved tolerability due to lack of binding by FcγRIII-III receptors, possibly due steric hindrance from the PEG side chain. Thus, HTI-1511 holds promise as a potentially safe and effective treatment of EGFR overexpressing tumors with KRAS or BRAF mutations.

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