JNJ-95437446: Discovery and Preclinical Characterization of an Amivantamab-based EGFRxMET-ADC for Solid Tumor Indications

Abstract LB473

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Abstract

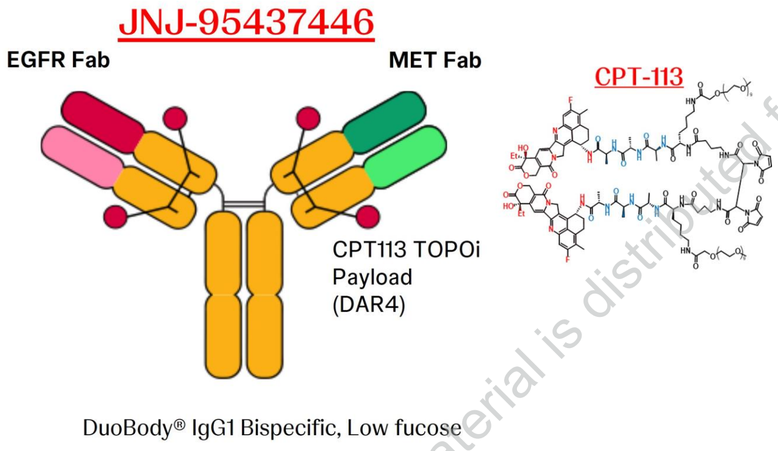
JNJ-95437446 is a potential best-in-class EGFR/MET bispecific antibody drug conjugate designed to deliver a cytotoxic payload to tumor cells while leveraging the unique characteristics of amivantamab. EGFR and MET are frequently expressed in solid tumors and amivantamab has demonstrated clinical efficacy in multiple non-small cell lung cancer (NSCLC) indications and is being studied in colorectal and head & neck carcinomas. Therefore, to assess the unique characteristics of JNJ-95437446, the ADC was evaluated in preclinical models of these tumor types.

JNJ-95437446 uses a dual-maleimide linker-payload, CPT-113 (Hangzhou DAC Biotechnology Co., Ltd.), to retain antibody stability upon conjugation and deliver a topoisomerase I inhibitor into tumor cells. Preclinical experiments demonstrated JNJ-95437446 retained amivantamab-like binding to EGFR and MET, induced rapid internalization, and produced potent, target-dependent cytotoxicity in vitro. Additionally, the released payload from the ADC was capable of bystander cytotoxicity. JNJ-95437446 resulted in potent efficacy, including complete tumor regressions, in preclinical cell line-derived NSCLC xenograft models of adenocarcinoma and squamous cell carcinoma, and in models resistant to amivantamab. In multi-dose GLP NHP safety assessment studies, JNJ-95437446 was well tolerated and pharmacokinetic analysis demonstrated favorable linker/payload stability.

JNJ-95437446 is an EGFR/MET-ADC exhibiting potent in vitro cytotoxicity and in vivo anti-tumor activity while being well-tolerated in a GLP NHP toxicity study. In summary, these data support development of JNJ-95437446 in a first-in-human clinical study (NCT07107230).

Background

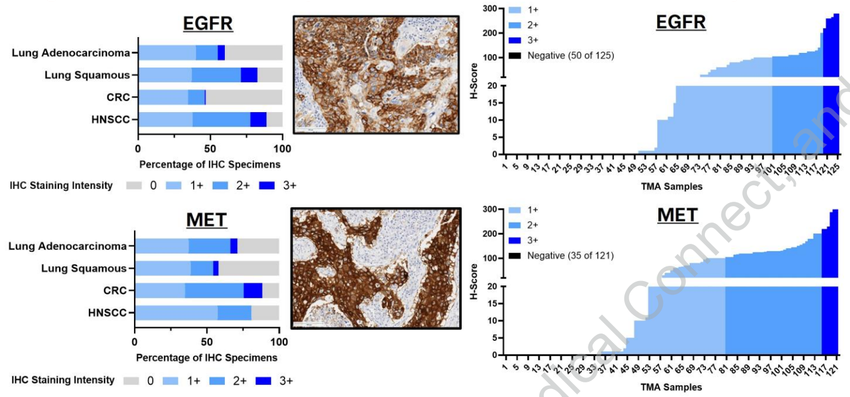
- JNJ-95437446 is an EGFR/MET-ADC based on amivantamab and conjugated to the dual-maleimide linker/payload CPT-113.
- EGFR mutations are frequent in NSCLC with MET overexpression conferring resistance to current EGFR-targeted therapies.
- Rybrevant® (amivantamab) is approved in EGFR mutated NSCLC and has demonstrated clinical efficacy in CRC and HNSCC.
- While not frequently mutated in other indications, both EGFR and MET are often highly expressed in multiple solid tumor indications including squamous cell carcinoma of the lung, CRC, and HNSCC.



Left: JNJ-95437446, an Amivantamab-based Antibody Drug Conjugate. Cross-linking of heavy-chains and light-chains by CPT-113 shown. Cytotoxic payload represented by red spheres. **Right:** CPT-113: Dual-maleimide conjugate (black), cleavable linker (blue), and cytotoxic payload (exatecan; red).

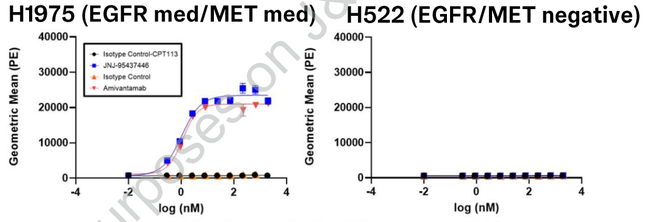
Results

Figure 1: EGFR and MET expression across solid tumors evaluated by IHC



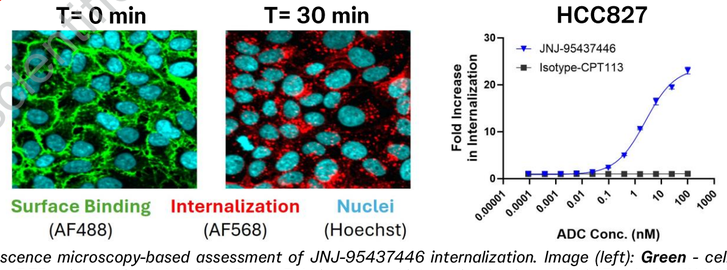
IHC-based evaluation of expression on TMAs from NSCLC, CRC, and HNSCC. Intensity of expression is depicted as 0 (negative), 1+ (weak), 2+ (moderate), and 3+ (strong). Graphs show the distribution of % positivity as well as staining intensity. Representative images showing IHC positivity (Magnification: 20X).

Figure 2: Binding JNJ-95437446 to EGFR/MET expressing cells



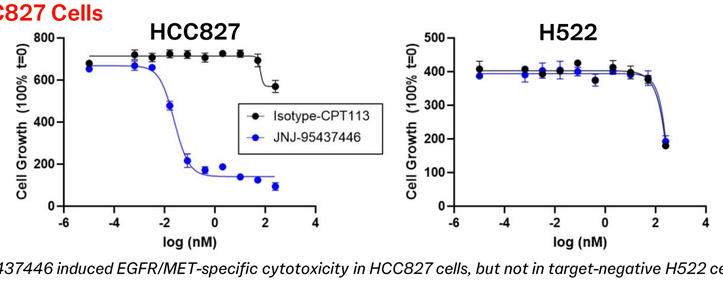
Flow-cytometry-based binding of JNJ-95437446 to EGFR/MET-expressing H1975 cells and absence of binding to target-negative H522 cells.

Figure 3: Internalization of JNJ-95437446 in HCC827 Cells



*Fluorescence microscopy-based assessment of JNJ-95437446 internalization. Image (left): **Green** - cell surface binding; **RED** – internalized JNJ-95437446. Fold increase of internalization into HCC827 cells by JNJ-95437446 compared to isotype control (right).*

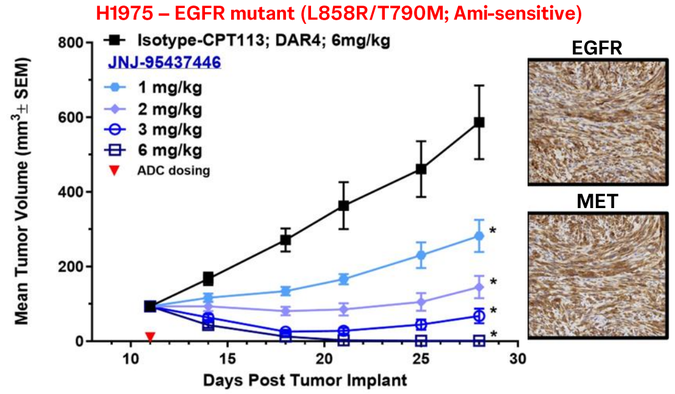
Figure 4: JNJ-95437446 Induces In vitro Cytotoxicity in EGFR Amplified HCC827 Cells



JNJ-95437446 induced EGFR/MET-specific cytotoxicity in HCC827 cells, but not in target-negative H522 cells.

Results

Figure 5: JNJ-95437446 Demonstrated Robust Efficacy in EGFR Mutant and KRAS Mutant NSCLC CDX Models



Nu/Nu mice bearing established H1975 (top) and H1373 (bottom) xenografts were dosed with a single IV injection of JNJ-95437446 or Isotype-ADC at the indicated concentrations and group tumor volumes are graphed as mean ± SEM. IHC shows EGFR and MET expression measured on ex vivo tumors.

* *p-value < 0.05*

Conclusion

- JNJ-95437446 is comprised of the topoisomerase linker/payload CPT-113 conjugated to the low-fucose human IgG1 EGFR/MET-targeting BsAb, amivantamab.
- Preclinical testing demonstrated the conjugation did not alter the biophysical profile or target-specificity of amivantamab.
- IHC confirmed prevalent expression of EGFR and MET on many solid tumors including NSCLC, CRC, and HNSCC.
- JNJ-95437446 rapidly internalized into EGFR and/or MET expressing cells and induced target-specific cytotoxicity in cell-based assays.
- Robust single-dose in vivo anti-tumor activity was observed in multiple NSCLC CDX and PDX models with diverse driver-mutations, including ones known to confer resistance to amivantamab, highlighting the novel ADC-based MOA of JNJ-95437446.
- The EGFR/MET BsAb ADC was well-tolerated when tested in a multi-dose IND-enabling cynomolgus monkey study.
- These data support the on-going clinical development of JNJ-95437446 in a first-in-human Phase I study in NSCLC, CRC, and HNSCC (NCT07107230).