IMGN151: A Next Generation Folate Receptor Alpha Targeting Antibody-Drug Conjugate Active Against Tumors with Low, Medium, and High Receptor Expression

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INTRODUCTION

Folate Receptor alpha (FRα) is an attractive antibody drug conjugate (ADC) target due to its over expression in multiple epithelial malignancies including ovarian, endometrial, triple negative breast, and non-small cell lung cancer, with limited expression on normal tissues.

IMGN853, a [38sarmavimab soravstatine, M9346A-sulfo-SPDB-DM4], a FRα targeting ADC, is currently in phase III (MIRASOL and SORAYA trials) clinical evaluation as monotherapy in patients with platinum-resistant epithelial ovarian cancer with high levels of FRα expression, building on the results from the prior randomized study, FORWARD I, which demonstrated the strongest treatment effects for IMGN853 in FRα-high disease (Moore, EMWO 2019).

In order to address the unmet needs of additional patient populations, we sought to develop a next generation FRα-targeting ADC active against tumors with a broad range of FRα expression. Development of a new molecular entity with the desired antitumor properties included optimization of the antibody format and the linker-payload.

The developed ADC, denoted IMGN151, comprises an asymmetric, bivalent, biparatopic antibody targeting two independent epitopes of FRα, linked to a highly potent maytansinoid derivative DM21 via a cleavable peptide linker. The average drug per antibody ratio is 3.5.

IMGN151 Structure

- BS527α: asymmetric biparatopic anti-FRα antibody comprised of IMGN853 arm and a scFv-arm targeting an independent epitope of FRα
- DM21-LG: new more potent maytansinoid-derived payload/linker

IMGN151 displays increased cytotoxic potency compared to IMGN853. This effect is most pronounced in cells with low to moderate levels of FRα expression:

- IMGN151 demonstrated better activity over IMGN853 against FRα low and positive cell lines, with the most

- Asymmetric biparatropic antibody boosts binding events and payload delivery
- A protease-cleavable linker improves stability and ADC half-life and exposure
- A highly potent payload DM21, which is released in a cell permeable form to provide enhanced bystander killing activity

IMGN151 preclinical profile warrants further development and advancement into the clinic.

CONCLUSIONS

- IMGN151 is a next generation of FRα-targeting ADC engineered to include multiple technological innovations to maximize the potential clinical benefit for patients with lower target expression:
  - Asymmetric biparatropic antibody boosts binding events and payload delivery
  - A protease-cleavable linker improves stability and ADC half-life and exposure
  - A highly potent payload DM21, which is released in a cell permeable form to provide enhanced bystander killing activity

- IMGN151 showed improved activity over IMGN853 in tumors with lower FRα expression:
  - In vitro, IMGN151 was more active against FRα-positive cell lines, with the most pronounced effect in cells with low to moderate levels of FRα
  - In vivo, IMGN151 demonstrated better activity over IMGN853 against FRα low and medium, and equivalent activity to IMGN853 against FRα high tumors with lower effective doses; tested doses were well tolerated
  - Cell lines/xenografts used for the studies originated from ovarian, endometrial, breast, and cervical cancer

- IMGN151 preclinical profile warrants further development and advancement into the clinic.

Abstract

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