Abstract 2890

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

Olga Ab, Laura M Bartle, Leanne Lanieri, Jose F. Ponte, Qifeng Qiu, Surina Sikka, Juliet A Costoplus, Wayne Deats, Nicholas C Yoder, Wayne C Widdison, Katie Mucciarone, Kate Selvitelli, Ying Chen, Neeraj Kohli, Thomas Chittenden, Richard Gregory, Yulius Setiady, Eric Westin

ImmunoGen, Inc., Waltham, MA

INTRODUCTION

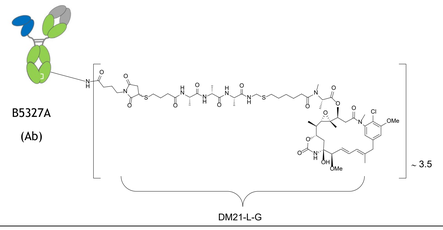
Folate Receptor alpha (FRα) is an attractive antibody drug conjugate (ADC) target due to its over expression in multiple epithelial malignancies including ovarian, endometrial, triple negative breast, and non-small cell lung cancer, with limited expression on normal tissues.

IMGN853 (mirvetuximab soravtansine, M9346A-sulfo-SPDB-DM4), a FRα targeting ADC, is currently in phase III (MIRASOL[1] and SORAYA[2] 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, ESMO 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



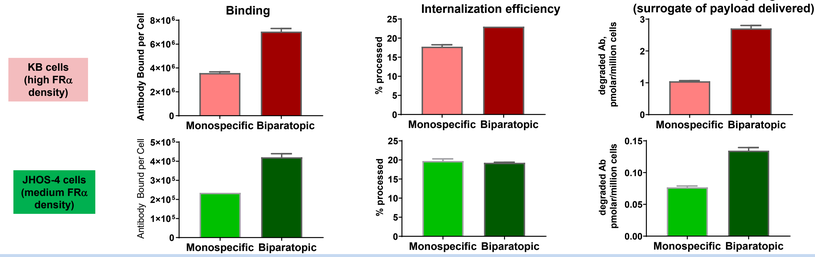
- B5327A: asymmetric biparatopic anti-FRα antibody comprises of IMGN853 arm and a scFv-arm targeting an independent epitope of FRα
- DM21-L-G: new more potent maytansine-derived payload/linker

References

1. ClinicalTrials.gov Identifier: NCT04209855
2. ClinicalTrials.gov Identifier: NCT04296890
3. Costoplus et. Al. (2019) "Peptide-Cleavable Self-immolative Maytansinoid Antibody-Drug Conjugates Designed To Provide Improved Bystander Killing". ACS Medicinal Chemistry Letters: 10, 1393–1399

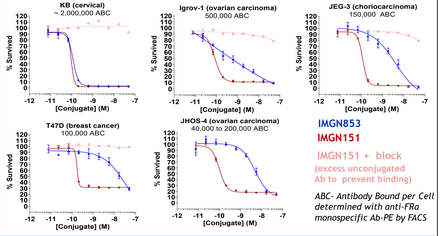
Antibody Processing

Monospecific = bivalent monospecific IgG1, antibody moiety of IMGN853; **Biparatopic** = antibody moiety of IMGN151



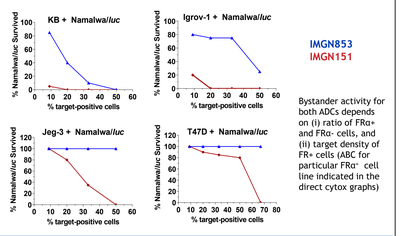
Biparatopic antibody boosts binding events leading to increased amount of antibody degraded (surrogate for amount of payload delivered/activated)

In Vitro Cytotoxic Activity



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

Bystander Killing Activity



IMGN151 releases hydrophobic catabolites leading to pronounced membrane permeability[3]. This, combined with increased payload delivery, results in potent bystander killing

Methods

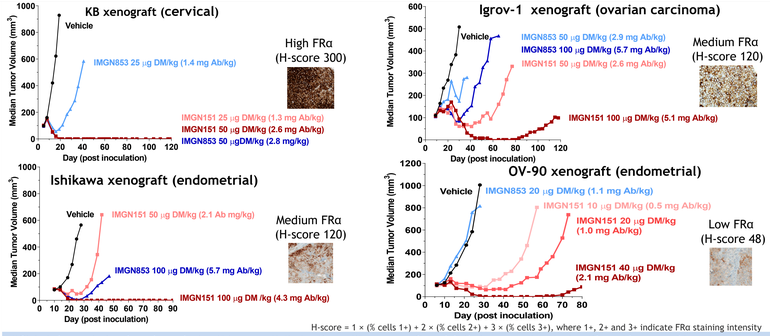
- **Antibody processing:** cells incubated with ^{3}H-Ab (5 nM) at RT for 20 min → unbound antibody removed → cells incubated at 37°C for 24 h, processed and ^{3}H-signal detected
- ***In vitro* cytox:** cells exposed to a range of ADC concentrations; cell viability measured after 5 days
- **Bystander killing activity:** mixed culture of FRα$^+$ and FRα$^-$ cells (Namalwa/*luciferase*) exposed to 0.5 nM ADC; Survival of FRα$^-$ luciferase$^+$ cells measured after 5 days
- **Pharmacokinetic:** ADC injected at 10 mg/kg, blood samples collected at certain time points, amount of DM-bound (ADC) measured by ELISA
- ***In vivo* efficacy:** ADC injected when tumor size reached ~ 130 mm^3 (single injection), tumor size measured twice a week and plotted vs time; payload-based doses indicated in the graphs

PK in Cynomolgus Monkeys

ADC PK parameters (Mean)	IMGN151	IMGN853
Cmax (µg/mL)	362	281
Vss (mL/kg)	59.6	42.2
Cl (mL/hr/kg)	0.3	0.4
Half-life (hr)	156	98.2
AUC$_{\infty}$(hr*µg/mL)	35400	25583

- IMGN151 has a terminal phase half-life ~ 60 hours longer than IMGN853
- IMGN151 has a total exposure ~40% higher than IMGN853
- Total antibody PK of the ADCs are similar, not shown

Efficacy *In Vivo*



H-score = 1 × (% cells 1+) + 2 × (% cells 2+) + 3 × (% cells 3+), where 1+, 2+ and 3+ indicate FRα staining intensity

IMGN151 demonstrates dose-dependent anti-tumor activity in FRα-positive xenograft models that represent patients with a wide range of target expression

- FRα -medium and -low xenograft models: IMGN151 is more active than IMGN853
- FRα -high model: IMGN151 showed equivalent activity to IMGN853 with lower effective dose
- All tested doses were well tolerated

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 biparatopic 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 dose; all 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

