Preclinical Evaluation of Mirvetuximab Soravtansine (IMGN853) Combination Therapy in Ovarian Cancer Xenograft Models

Abstract C170

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INTRODUCTION

The current treatment paradigm for epithelial ovarian cancer (EOC) includes platinum based doublet regimens until resistance followed by combination chemotherapy plus bevacizumab and then subsequent lines of cytotoxic monotherapy. However, there are still over 14,000 deaths due to ovarian cancer per year in the US highlighting the significant need for new therapies.

Mirvetuximab soravtansine (IMGN853) is an antibody-drug conjugate consisting of the cytotoxic maytansinoid, DM4, covalently linked to the humanized monoclonal antibody M9346A, which selectively binds to folate receptor alpha (FRα). IMGN853 is currently being evaluated as monotherapy in FRα-positive solid tumors in a Phase 1 trial (NCT01609556), with encouraging results recently reported in 17 evaluable patients with platinum-resistant EOC treated at 6.0 mg/kg adjusted ideal body weight (AIBW) IV every 3 weeks (Moore K et al, 2015). In this cohort, preliminary analysis suggests a correlation between FRα expression level and IMGN853 anti-tumor activity (*Abstract #C47, L. Martin).* A Phase II trial (FORWARD I) assessing IMGN853 for 4th or 5th line treatment of EOC is scheduled to begin in 2015.

Here we report our findings of preclinical studies assessing single agent and combination therapy activity of IMGN853 in ovarian cancer xenograft models. The efficacy observed in these models suggests that IMGN853 in combination with pegylated liposomal doxorubicin (PLD), or bevacizumab and/or carboplatin may be promising regimens to evaluate in clinical trials of EOC both in the relapsed and upfront settings. A phase1b clinical study (FORWARD II) assessing doublet combinations of IMGN853 with PLD, bevacizumab and carboplatin in relapsed EOC is planned for 2015.

Mirvetuximab Soravtansine Mechanism of Action

AN INTEGRATED SYSTEM

Linker
- Cleavable linker stable in the blood stream
- Bystander killing of neighboring cancer cells

Ultra-potent anticancer agent
- DM4 – a potent tubulin-targeting agent

Antibody (Ab)
- A folate receptor α (FRα)-binding antibody

Target
- Appropriate for an ADC
- Highly expressed in ovarian and other cancers

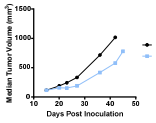
Methods

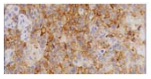
***In vivo* efficacy studies:**

Female immuno-compromised mice bearing subcutaneous ovarian xenograft tumors (average tumor volume 100-150 mm^3, 6-10 animals per group) were treated as described in the Tables. Tumors were measured twice weekly with volume calculated as either (length x width x height)/2 for OV90 studies or (length x width^2)/2 in PDX studies. A mouse was considered to have a partial regression (PR) when tumor volume was reduced by 50% or greater and to have a complete regression (CR) when no palpable tumor could be detected. Tumor growth inhibition (T/C %) was calculated as the ratio of median tumor volumes at the time when control tumors reached a predetermined size in mm^3. (Bissery, M. et al., Cancer Research, 51; 4845-52, Sept. 1991)

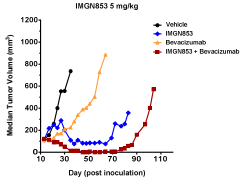
Combination with Bevacizumab (OV90)

OV90 HGSOC Platinum Resistant Model





FRα 1-3 Heterogeneous

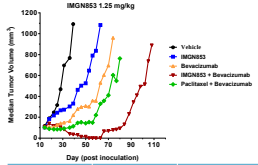


IMGN853 and bevacizumab were both active in the model as single agents with few regressions

Combination IMGN853 + bevacizumab was highly active in the model with complete tumor regressions observed in all mice

All IMGN853 +/- bevacizumab therapies were well tolerated

Treatment	Dosing	T/C (%)	CR	Result
IMGN853	5 mg/kg 1X	36	1/5	Active
Bevacizumab	5 mg/kg 1X	37	0/6	Active
IMGN853 + Bevacizumab	5 mg/kg 1X 5 mg/kg 1X	9	6/6	Highly Active



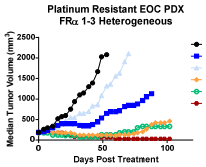
Strong anti-tumor activity of IMGN853 + bevacizumab even at a dose where single agent IMGN853 is only minimally active.

1.25 mg/kg IMGN853 + bevacizumab dosed 1X was more active than 10 mg/kg paclitaxel + bevacizumab (5% vs 12% T/C and 5/8 CR vs 0/8 CR)

All IMGN853 +/- bevacizumab therapies were well tolerated

Treatment	Dosing	T/C (%)	CR	Result
IMGN853	1.25 mg/kg 1X	37	0/7	Active
Bevacizumab	5 mg/kg 1X	22	0/8	Active
IMGN853 + Bevacizumab	1.25 mg/kg 1X 5 mg/kg 1X	5	5/8	Highly Active
Paclitaxel + Bevacizumab	10 mg/kg 5 mg/kg	12	0/8	Active

Combination with Bevacizumab (PDX Model)



Single agent IMGN853 was more active than paclitaxel in this EOC PDX model

Single agent bevacizumab was highly active in this model, however no regressions were observed

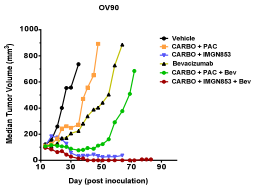
Combination IMGN853 + bevacizumab resulted in most mice having partial regression of tumors

On the last day of the study, the median tumor volume of the IMGN853 + bevacizumab treatment group was 37 mm^3 compared to 463 and 651 mm^3 in the paclitaxel + bevacizumab and monotherapy bevacizumab groups, respectively

All IMGN853 +/- bevacizumab therapies were well tolerated

Treatment	Dosing	T/C (%)	PR	Result
IMGN853	5 mg/kg QWx2	31	0/8	Active
Paclitaxel	10 mg/kg QWx2	71	0/8	Inactive
Bevacizumab	5 mg/kg QWx2	6	0/8	Highly Active
Paclitaxel + Bevacizumab	10 mg/kg QWx2 5 mg/kg QWx2	6	6/8	Highly Active
IMGN853 + Bevacizumab	5 mg/kg QWx2 5 mg/kg QWx2	3	7/8	Highly Active

Combination with Carboplatin and Bevacizumab



Strong anti-tumor activity of carboplatin + IMGN853 was observed in the OV90 EOC model.

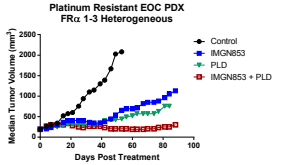
Carboplatin + IMGN853 was more active than carboplatin + paclitaxel and carboplatin + paclitaxel + bevacizumab

Triple combination consisting of carboplatin + IMGN853 + bevacizumab resulted in complete regression of tumors in all mice

All IMGN853 +/- bevacizumab therapies were well tolerated

Treatment	Dosing	T/C (%)	CR	Result
Carboplatin + Paclitaxel	100 mg/kg 1X 10 mg/kg 1X	45	0/6	Inactive
Carboplatin + IMGN853	100 mg/kg 1X 5 mg/kg 1X	10	3/6	Highly Active
Bevacizumab	5 mg/kg 1X	37	0/6	Active
Carboplatin + Paclitaxel + Bevacizumab	100 mg/kg 1X 10 mg/kg 1X 5 mg/kg 1X	16	1/6	Active
Carboplatin + IMGN853 + Bevacizumab	100 mg/kg 1X 5 mg/kg 1X 5 mg/kg 1X	5	6/6	Highly Active

Combination with Pegylated Liposomal Doxorubicin



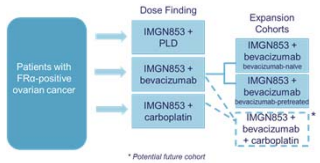
QWx2 dosing of IMGN853 demonstrated comparable activity to PLD in this platinum resistant EOC PDX model

Combination IMGN853 + PLD was highly active in the model

All IMGN853 +/- PLD therapies were well tolerated

Treatment	Dosing	T/C (%)	Result
IMGN853	5 mg/kg QWx2	31	Active
PLD	4 mg/kg QWx2	21	Active
IMGN853 + PLD	5 mg/kg QWx2 4 mg/kg QWx2	10	Highly Active

FORWARD II Clinical Trial



CONCLUSIONS

- Combinations of IMGN853 with bevacizumab or PLD were substantially more effective than monotherapy in models of platinum resistant EOC.
- IMGN853 + bevacizumab therapy was found to be highly active even at doses where single agent IMGN853 was minimally active.
- Carboplatin + IMGN853 was more efficacious than the triple combination of carboplatin + paclitaxel + bevacizumab in the OV90 EOC xenograft model.
- Carboplatin + IMGN853 + bevacizumab was highly active with all mice having tumors that completely regressed.
- The efficacy observed in these models suggests that IMGN853 in combination with PLD, or bevacizumab and/or carboplatin may be promising regimens and warrant evaluation in clinical trials of EOC both in the relapsed and upfront settings.
- A phase1b clinical study (FORWARD II) assessing doublet combinations of IMGN853 with PLD, bevacizumab and carboplatin in relapsed EOC is planned for 2015.

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