Safety, Pharmacokinetics and Efficacy of IMCgp100, a First-in-Class Soluble TCR Anti-CD3 Bispecific T Cell Redirector With Solid Tumour Activity: Results From the FIH Study in Melanoma

Abstract # 3016

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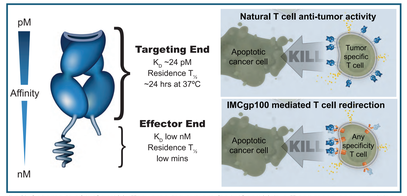
BACKGROUND

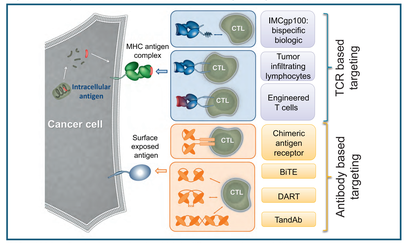
- IMCgp100 is a first-in-class bispecific biologic known as a T cell redirector
- The molecule contains two functional ends: the targeting end is a soluble affinity enhanced T Cell Receptor (TCR) and the effector end is an anti-CD3 scFv
- IMCgp100 binds, with picomolar affinity, a gp100 peptide in the context of HLA-A2; the anti-CD3 scFv end binds and activates proximal CD3+ T cells
- Gp100 is a differentiation antigen expressed in melanocytes and overexpressed in melanoma tumors; uveal melanoma tumors express this antigen at high levels more consistently compared to cutaneous melanoma tumors
- *In vitro*, IMCgp100 binds HLA-A2+/gp100+ melanoma cells causing redirection of T cell cytotoxicity and the induction of broad and potent immune effects

Figure 1. Schematic of IMCgp100 and Mode of Action



(Left) Schematic of IMCgp100. The targeting system for IMCgp100 is a T cell receptor recognizing an HLA-A2 (does not bind non-A2 HLA type) restricted peptide of the gp100 antigen. The TCR was cloned from a human T cell and the affinity of the TCR for its peptide:HLA complex was increased ~3 million-fold. IMCgp100 is approximately 75 kDa in size and manufactured in E. coli; (Right-top) Natural anti-tumor activity requires tumor specific T cells; (Right-bottom) IMCgp100 re-directs T cells of any specificity (eg tumor or viral specific) against tumor cells.

Figure 2. IMCgp100 is a Unique T Cell Redirecting Biologic Therapeutic



IMCgp100 is a first in class molecule which is different to other modalities.

METHODS

- The Phase I was conducted in HLA-A2+ patients with advanced melanoma, using a 3+3 design to define the Maximum Tolerated Dose (MTD)
- Patients were treated with IMCgp100 (iv) once a week (QW, Arm 1) or x4 days dosing repeated every 3 weeks (4QD3W, Arm 2) to evaluate safety, pharmacokinetics and efficacy
- A total of 84 patients were treated
- Data cut: 29th April 2016
- Objectives:
  - Primary: to evaluate safety and tolerability of IMCgp100
  - Secondary: to characterize IMCgp100 pharmacokinetics, changes in tumor burden (by RECIST 1.1 criteria) and evaluate the incidence of anti-IMCgp100 antibodies

RESULTS

Arm 1

- Arm 1 dose escalation treated 31 patients from 5ng/kg to 900ng/kg
- Arm 1 QW MTD was determined to be 600ng/kg and a recommended phase 2 dosing regimen (RP2D-QW) was defined
- In Arm 1 dose-limiting toxicity (DLT) of grade 3 or 4 hypotension was observed
- It is hypothesized that hypotension is a consequence of the following:
  - IMCgp100 targeting of gp100+ skin melanocytes resulting in localized T cell activation and chemokine release (see **Figure 8**)
  - T cells trafficking from the periphery (see **Figure 4**) into tissues resulting in observed fluid shifts, leading to hypotension

Dose Level (ng/kg)	N (patients)	DLT Observed
5	3	—
15	3	—
45	3	—
135	3	—
270	3	—
405	6	One grade 3 hypotension[a]
600	6	One grade 4 hypotension[a]
900	4	Two grade 3 hypotensions[a]

DLT = dose limiting toxicity.
[a]Grade 3 and 4 hypotension was associated with a significant and rapid decrease in peripheral lymphocyte count.

Pharmacokinetics

- IMCgp100 has an approximately dose-proportional profile with a plasma $T_{1/2}$ of 5 – 6 hrs at the RP2D

Safety

Table 1. IMCgp100 Related AE Observed in ≥10% of Patients by CTCAE Grade, QW Dosing

System Organ Class/Preferred Term	All Grades N=66	Grade 3 or 4 N=66
Rash	45 (68%)	10 (15%)
Pruritus	42 (64%)	0
Pyrexia	34 (52%)	3 (5%)
Periorbital oedema	30 (46%)	0
Fatigue	28 (42%)	0
Nausea	26 (39%)	0
Hypotension	19 (29%)	6 (9%)
Skin exfoliation	19 (29%)	0
Vomiting	19 (29%)	0
Rash maculo-papular	16 (24%)	2 (3%)
Chills	16 (24%)	1 (2%)
Erythema	16 (24%)	0
Dry skin	15 (23%)	0
Headache	14 (21%)	0
Lymphopenia	13 (20%)	9 (14%)
Face oedema	13 (20%)	0
Flushing	11 (17%)	1 (2%)
Influenza like illness	9 (14%)	0
Oedema peripheral	9 (14%)	0
Vitiligo	9 (14%)	0
Rash erythematous	8 (12%)	3 (5%)
Decreased appetite	7 (11%)	0
Hair colour changes	7 (11%)	0
Tachycardia	7 (11%)	0

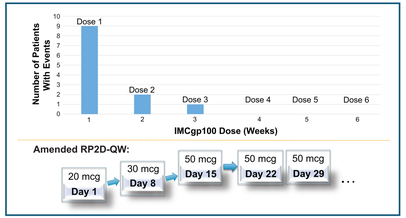
Table 2: Patient Baseline Demographic

		All Patients* Total (N=84)	Uveal Patients Total (N=16)
Gender	Male	54 (64%)	10 (63%)
	Female	30 (36%)	6 (38%)
Age	Median (range)	60 (25-78)	60 (39-71)
Performance status	PS 0	54 (64%)	10 (63%)
	PS 1	30 (36%)	6 (38%)
Prior therapy	Median prior systemic therapies (range)	4 (1-20)	3 (1-9)
	Prior chemotherapy	46 (55%)	11 (69%)
	Prior immunotherapy	26 (31%)	5 (31%)
	Prior radiotherapy	34 (41%)	10 (63%)
	Prior surgery	70 (83%)	14 (88%)
	Other	26 (31%)	4 (25%)
Stage at screening	IIIB	3 (4%)	0 (0%)
	IV	81 (96%)	16 (100%)
LDH high		33 (39%)	10 (67%)
Liver tumor burden		32 (38%)	13 (87%)

*Includes 16 uveal, 1 mucosal and 67 cutaneous melanoma patients.

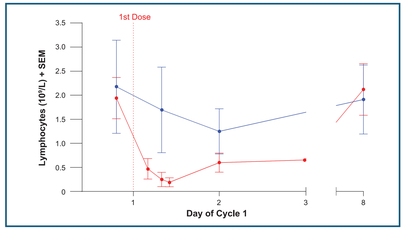
RP2D-QW Dosing Format

Figure 3. Observation of Toxicities Which Include Severe and/or Serious Hypotension Confined to the First Weeks of Dosing



RP2D-QW format amended to include flat dosing and intra-patient dose escalation to mitigate risk of first challenge toxicities.

Figure 4. Lymphocytes Traffic From Periphery Following First Dose of IMCgp100; This is More Profound in Cases With Severe and/or Serious Hypotension



Mean peripheral lymphocyte counts in blood at baseline (day 1 pre-dose) and at various time-points following the first dose of IMCgp100 (4h, 8h and/or 10h, 24h, 48h and day 8 post-dose) in a patient group with reported severe and/or serious hypotension (●, n=6) compared to a patient group with no reported hypotension (●, n=5). Point of dosing indicated. Day 8 sample is pre-second dose.

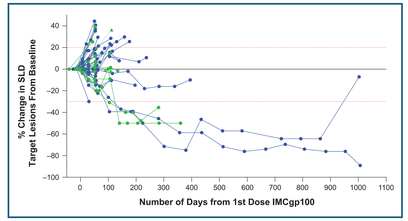
Preliminary Tumor Response – Arm 1 (QW)

- Of the 66 patients (non-uveal n=50; uveal n=16) treated in Arm 1, a cohort of 47 patients was considered evaluable for response assessment. Patients were considered evaluable if treated with at least one dose of IMCgp100 at ≥270ng/kg (starting from a median absolute dose of 16mcg) or the RP2D-QW and have had at least one end of cycle scan (with a minimum interval of 8 weeks) or discontinued prior to the scheduled scan
- Partial responses were durable and seen in patients refractory to checkpoint agents

Table 3. Preliminary Response Data

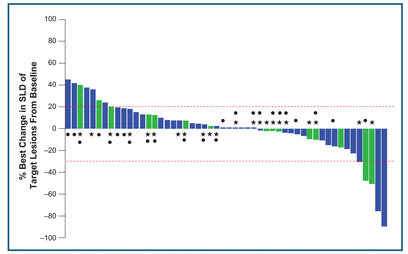
	Non-uveal	Uveal
Evaluable patients – n	33	14
Best overall response – n (%)		
Complete response (CR)	0 (0)	0 (0)
Partial response (PR)	2 (6)	2 (14)
Stable disease (SD)	6 (18)	8 (57)
Stable disease with minor response (SLD <–10%)	3 (9)	0 (0)
Progressive disease (PD)	20 (61)	4 (29)
Discontinued prior to first scan	2 (6)	0 (0)
Overall response rate (CR or PR) – n (%)	2 (6)	2 (14)
Disease control rate (CR or PR or SD at ≥ 16 weeks) – n (%)	7 (21)	8 (57)

Figure 5. Spider Plot of a Cohort of 52 Patients Treated at ≥270ng/kg or the RP2D



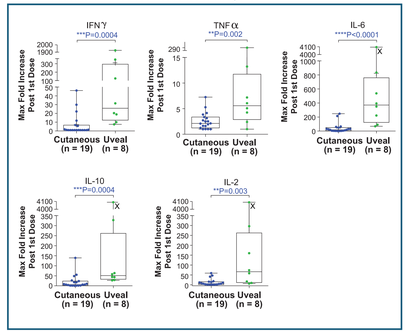
● Non-uveal (n=37); ● Uveal (n=15); includes 2 uveal patients (▲) where measurements were made with both CT and MRI scan. This plot includes 7 patients not included in Table 3 since they had one dose then only a 4-week scan before coming off-study due to DLT, PD, or were placed on other therapies at PI discretion.

Figure 6. Waterfall Plot of a Cohort of 52 Patients Treated With IMCgp100 ≥270ng/kg or at the RP2D



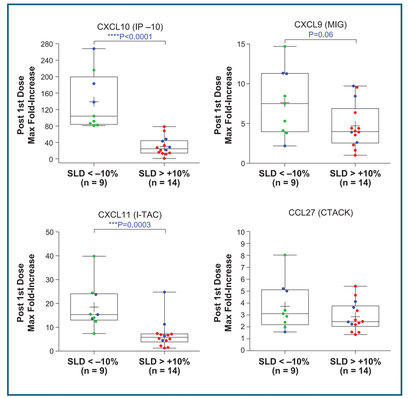
■ Non-uveal (n=37); ■ Uveal (n=15). Patients with Liver (★) lesions and/or high baseline LDH (●, ≥ 239 U/L) are annotated. This plot includes 7 patients not included in Table 3 since they had one dose then only a 4-week scan before coming off-study due to DLT, PD, or were placed on other therapies at PI discretion.

Figure 7. Biological Differences Found Between Cutaneous and Uveal Melanoma Patients in First Dose Response to IMCgp100



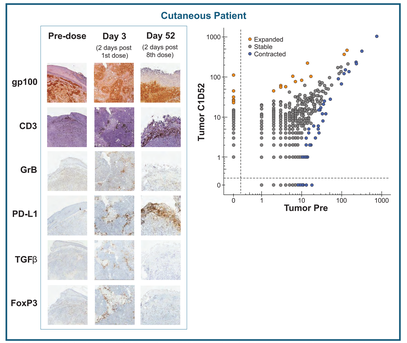
Maximum fold increase in serum levels of indicated cytokines following the first dose of IMCgp100 in a group of cutaneous patients (●, n=19) compared to uveal melanoma patients (●, n=8). It is hypothesized that measured cytokines are a consequence of on-target tissue activity which is detected in serum. For one uveal patient (X) maximum increase in IL-2, IL-6 and IL-10 was above the upper limit of quantification (ULOQ) for assay; fold change value at ULOQ is shown. Box plot: bar shows median, hinges indicate 25 to 75 percentile, whiskers show min and max; '+' indicates mean value. Statistical comparison by Mann-Whitney test.

Figure 8. Changes in Anti-Tumor (CXCL9, 10 11) but not Skin Homing Chemokine (CCL27) Following the First Dose of IMCgp100 is Associated With Tumor Shrinkage



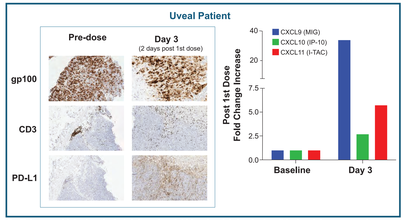
Maximum fold increase in serum levels of indicated chemokines following the first dose of IMCgp100 in patient group showing a reduction in target tumor lesion SLD by at least 10% (●, SLD < -10%, n=9) compared with patient group showing an increase by 10% or more (●, SLD > +10%, n=14); uveal patients annotated (●); Box plot: bar shows median, hinges indicate 25 to 75 percentile, whiskers show min and max; '+' indicates mean value. Statistical comparison by un-paired t-test or Mann-Whitney test.

Figure 9. Analysis of Biopsies From Cutaneous Melanoma Patient Reveals IMCgp100 Induced Intra-Tumoral Adaptive Response With Expansion of New and Pre-Existing Clones



(Left) Immunohistochemical staining of serial biopsies (postauricular lesions) from a patient on IMCgp100 treatment. Markers tested are indicated. (Right) T cell repertoire analysis measured by TCR-β chain sequencing (Adaptive Biotechnologies) in baseline and on treatment (Day 52) tumour samples from patient (each dot = 1 unique clone).

Figure 10. T Cell Infiltration in Uveal Melanoma Patient Biopsy Following IMCgp100



(Left) Immunohistochemical staining of serial biopsies (abdominal wall lesions) from a uveal melanoma patient (Right) gene expression analysis of the chemokines CXCL9, CXCL10 and CXCL11 in baseline and on treatment (Day 3) tumour biopsies from patient, measured using the Nanostring nCounter Analysis System.

CONCLUSIONS

- IMCgp100 is a first-in-class TCR anti-CD3 scFv bispecific T cell redirector with a favourable safety profile and preliminary evidence of durable responses in melanoma (cutaneous and uveal melanoma)
- Higher increases in antitumor chemokines post first dose are associated with tumor shrinkage
- Pharmacodynamic data shows IMCgp100 induces T cell infiltration into tumors (cutaneous and uveal melanoma) and provides supportive evidence for planned combination strategies (eg with anti-PDL1 and anti-TGFb therapies)
- Data supports immune combination development in cutaneous melanoma
- Data supports monotherapy development in uveal melanoma
- Continued exploration of dose, dosing regimen and pharmacodynamic correlates with safety and efficacy ongoing in further development

Presented at ASCO, Chicago, Illinois on the 5th June 2016