Five Year Survival in Patients with Metastatic Melanoma Receiving IMM-101

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Background

- Immunotherapies such as ipilimumab, nivolumab and pembrolizumab alone and in combinations have provided durable benefits in metastatic melanoma, increasing five-year survival to around 20%[1].
- IMM-101, a systemic immunomodulator containing heat-killed *Mycobacterium obuense* (NCTC13365), enhances the innate immune response and, in an animal model, increases the number of CD8+ cytotoxic lymphocytes.
- In a randomised Phase 2 study, IMM-101, in combination with gemcitabine, increased overall survival in patients with metastatic pancreatic cancer compared to gemcitabine alone (NCT01303172).
- Five year survival information is now available for patients with metastatic melanoma recruited to an earlier Phase 1 study of IMM-101.

[1] McDermott *et al.*, Cancer Treatment Reviews 40 (2014) 1056-1064.

Statistical Methods

Baseline
- Patient demographics and disease history for both study cohorts at time of entry to each study.

Efficacy
- Efficacy endpoint in LTF study is overall survival (OS) (if patient withdraws, consent sought for continued data collection on survival). OS presented for all patients completing FIH study.

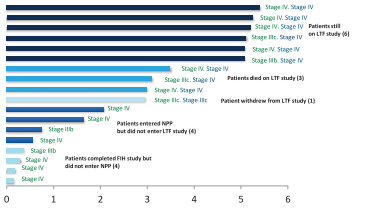
Exposure
- Time on IMM-101 treatment for all patients completing FIH study.

Treatments
- All IMM-101 administrations presented for all patients entering the LTF study.
- Other anti-cancer treatments whilst receiving IMM-101 presented for all patients entering the LTF study.

Safety and Tolerability
- IMM-101-related adverse events (AEs) reported during IMM-101 treatment in FIH and LTF studies, presented for patients completing FIH and for patients entering LTF study.
- Relevant medical events during NPP treatment presented for patients entering LTF study.

All data reported to a cut-off date of 26 August 2015.

Survival and Censoring of Patients



Green = Stage of disease at time of entry into FIH study, Blue = Stage of disease at time of entry into LTF study.

Time on IMM-101 Treatment

All patients completing FIH study

Patient Sub-group	Exposure (months)
Patients completing FIH study only (N=5)	
Median (range)	0.95 (0.9 to 1.0)
Patients completing FIH study and taking at least one IMM-101 dose during NPP only (N=3)	
Median (range)	19.7 (9.0 to 24.9)
Patients completing FIH study, continuing into NPP and enrolled into LTF study (N=10)	
Median (range)	56.7 (32.4 to 62.4)
Exposure = (last IMM-101 dose date or date of last NPP order – first IMM-101 dose date+1)/30.4375.	

IMM-101 Related Adverse Events

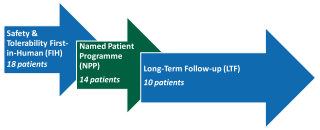
Following first IMM-101 dose in FIH with incidence ≥ 10% in either cohort

Adverse Event (MedDRA Preferred Term)	All patients completing FIH study Incidence n (%) N=18	All patients entering LTF study Incidence n (%) N=10
Patients with at least 1 treatment related AE	15 (83%)	8 (80%)
Injection site reaction	7 (39%)	6 (60%)
Injection site pain	5 (28%)	3 (30%)
Influenza like illness	5 (28%)	2 (20%)
Injection site discharge	5 (28%)	3 (30%)
Injection site pruritus	3 (17%)	2 (20%)
Arthralgia	3 (17%)	2 (20%)
Pyrexia	3 (17%)	0
Injection site ulcer	2 (11%)	1 (10%)
Pain in extremity	2 (11%)	0
Pain	2 (11%)	1 (10%)
Headache	2 (11%)	1 (10%)
Other AEs with incidence 10% in patients entering LTF study	Peripheral swelling; Musculoskeletal pain; Back pain; Erythema; Myalgia; Night sweats; Skin mass; Injection site abscess, Skin bacterial infection; Lymphadenopathy; Skin ulcer	

- **All related AEs reported as mild or moderate, except 1 report of injection site pruritus (in 1 patient who participated in the FIH study only).**
- **No treatment-related serious AEs were reported.**

Methods

- Between March and July 2010, 18 patients with metastatic melanoma (12 Stage IV, 3 Stage IIIc and 3 Stage IIIb) completed a first-in-human (FIH) study to evaluate the safety and tolerability of IMM-101 (NCT01308762).
- Patients could then receive IMM-101 treatment on a named patient basis (NPP) from November 2010.
- From February 2012, patients could enter an open label long-term follow-up (LTF) study (NCT01559818), which is still ongoing.



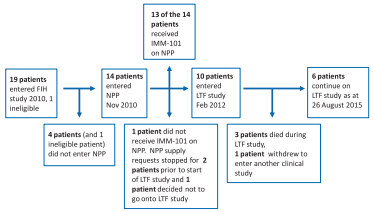
First-in-human (FIH) study

- To evaluate safety and tolerability of intra-dermal injections of IMM-101 in melanoma cancer patients.
- Three doses of IMM-101 (0.1 mg, 0.5 mg or 1.0 mg) given by intradermal injection at 2-weekly intervals after an initial placebo dose, each evaluated in sequential cohorts of 6 patients.

Long-term follow-up (LTF) study

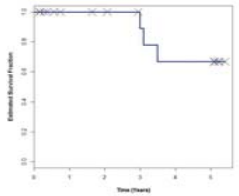
- To determine long-term safety profile of IMM-101 over extended use.
- Intradermal injection of 1.0 mg IMM-101 (10 mg/mL solution) into skin overlying deltoid muscle, alternate arms at each dose. One dose every 4 weeks, with modification at investigator discretion (dosing interval ≥ 14 days).
- At start of LTF study, written informed consent was obtained to retrospectively collect disease and treatment history whilst on NPP treatment.

Patient Flow



Overall Survival Kaplan–Meier Curve

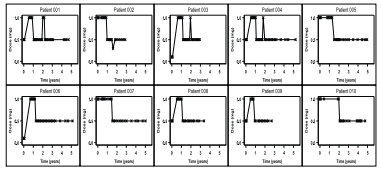
All patients completing FIH study



X denotes patient alive at last known contact date.

IMM-101 Administration

All patients entering LTF study – time by IMM-101 dose taken



- **Initial IMM-101 dose dependent on FIH cohort allocation according to enrolment order: 0.1 mg (2 patients); 0.5 mg (4 patients); 1.0 mg (4 patients).**
- **Dosing and frequency during NPP based on management of injection site reactions.**
- **All patients had history of injection site reactions at entry to LTF study.**
- **During LTF study, patients continued IMM-101 treatment at NPP dose, at investigator discretion.**

Significant Medical Events During NPP Treatment

All patients entering LTF study

Event (MedDRA Preferred Term)	Incidence n (%) N=10
Injection site reaction	8 (80%)
Injection site ulcer	1 (10%)
Pulmonary mass	1 (10%)
Skin lesion	1 (10%)
Epistaxis	1 (10%)
Abdominal tenderness	1 (10%)
Bronchial polyp	1 (10%)
Pregnancy	1 (10%)
Cancer treatment procedures are reported in anti-cancer concomitant therapies.	

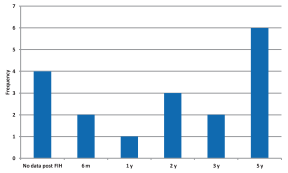
Patient Characteristics

At entry to FIH and LTF studies

		FIH Study[1]	LTF Study
Total patients enrolled		19 (100%)	10 (100%)
Age at each study entry (y)	Median (range)	59 (26 - 79)	70.5 (33 - 81)
Gender	Male	11 (58%)	6 (60%)
	Female	8 (42%)	4 (40%)
Melanoma Disease Stage (at each study entry)	Stage III b	3 (16%)	0
	Stage III c	3 (16%)	1 (10%)
	Stage IV	13 (68%)	9 (90%)
Performance Status		(Not collected)	0: Asymptomatic (100%)
Time Since Diagnosis of current melanoma presentation at each study entry (y)	Median (range)	4.12 (0.4 - 37.5)	6.56 (3.1 - 39.0)

[1]18 patients received all 3 doses of IMM-101, 1 patient was withdrawn from the study due to a protocol violation (pre-existing brain metastases) and received two doses of IMM-101 at the initial 0.5 mg dose.

Frequency of Survivors by Year Following First IMM-101 Treatment



Survival time reflects the minimum survival time, accounting for patient deaths and last known contact date in survivors.

Concomitant Anti-Cancer Therapies

All patients entering LTF study

Anti-Cancer Therapy	Incidence n (%) N=10
Number of patients with at least one anti-cancer concomitant therapy	9 (90%)
Anti-cancer surgery	8 (80%)
Chemotherapy Bleomycin, electrochemotherapy (1); Carboplatin, Dacarbazine (1); Low dose Naltrexone, Melphalan (1); cyclophosphamide (1)	4 (40%)
Radiotherapy	3 (30%)
Immunotherapy	3 (30%)
Interleukin-2	2
Ipilimumab	1
TNF Alpha	1
Radiofrequency ablation	2 (20%)

- All anti-cancer therapies received on or after first IMM-101 dosing throughout entire treatment course.
- Anti-cancer surgery includes all cancerous lesion removals.
- No patients received other anti-cancer therapy during FIH study.

Conclusions and Discussion

- 6 of the 18 (33.3%) patients with Stage III/IV melanoma at enrolment to FIH study in 2010 and not lost to follow-up, are alive and on study at five years.
- All of the 6 patients alive and on study at five years had Stage IV disease when entering into the LTF study between February and June 2012.
- IMM-101 was well tolerated when administered over 5 years to patients with metastatic melanoma - treatment-related AEs were most commonly injection site reactions, of which only one was considered severe. There were no treatment-related SAEs.
- Majority of LTF patients received other anti-cancer therapies whist on NPP and in LTF study including surgery (n=8) and chemotherapy (n=4).
- All patients in LTF study now receiving a dose reduction of 0.5 mg IMM-101, at investigator discretion.

These data, together with those of the previously reported pancreatic cancer study, indicate that IMM-101 has the potential to be effective in different tumour types.

Acknowledgements

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