# IMAGE 1: A MULTI-CENTER RANDOMIZED, OPEN-LABEL, PROOF OF CONCEPT, PHASE II TRIAL COMPARING GEMCITABINE WITH AND WITHOUT IMM-101 IN ADVANCED PANCREATIC CANCER

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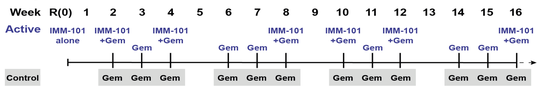
## BACKGROUND

- There is an urgent need for pancreatic cancer treatments which improve survival without adversely affecting safety and quality of life.
- IMM-101 is a systemic immunomodulator which induces protective CD8+ T cell responses and reduces metastatic burden in murine models of pancreatic cancer (Elia *et al*., 2013).
- It is a suspension of heat-killed whole cell *Mycobacterium obuense* (NCTC13365) in borate-buffered saline, administered intradermally.
- It has been shown to be safe and well-tolerated in a Phase I safety and tolerability trial in patients with Stage IIIb/IV melanoma (NCT01308762) (Stebbing *et al.*, 2012).
- Here we report results of a Phase II trial in advanced pancreatic cancer (NCT01303172).

## METHODS

- The purpose of this proof of concept Phase II study was to direct future development of IMM-101 in pancreatic cancer.
- Patients were randomly assigned in a 2:1 ratio to receive IMM-101 (0.1mL intradermal injection of 10mg/mL) + Gem (1000mg/m$^2$) or Gem alone according to the schedule described in Figure 1.
- Per protocol this could be continued to a 12-cycle maximum.

**Figure 1: Treatment Schedule**




### Key Eligibility Criteria

- ≥18 years of age
- Confirmed inoperable ductal adenocarcinoma of the pancreas with or without metastatic disease
- Measurable lesions in at least one site which has not been previously irradiated
- WHO performance status of 0-2
- Serum albumin >26 g/L
- Serum C-reactive protein (CRP) <70 mg/L
- No previous chemotherapy treatment for pancreatic cancer
- Life expectancy of >3 months from randomization

- There were 22 sites in 5 countries and randomization of 110 patients from 142 screened was completed in July 2013, distributed as follows: Spain 45%; UK 29%; Italy 19%; Cyprus 5% and Ireland 2%. The treatment phase of the study ended in July 2014.

### Analysis and Reporting of Results

- Primary efficacy endpoint was overall survival (OS)
- Safety, tolerability and progression free survival (PFS) also reported
- OS, PFS reported for Intent-to-treat (ITT) and per protocol (PP) sets and metastatic sub-groups of these sets
- Safety and tolerability endpoints analyzed using the Safety Set

**Table 1: Analysis Sets and Sub-groups (patient numbers)**

| Set | | All | Metastatic | Composition |
|---|---|---|---|---|
| ITT | Total | 110 | 92 | All randomized patients |
| | Gem | 35 | 28 | |
| | IMM-101 + Gem | 75 | 64 | |
| PP | Total | 98 | 82 | Exclusions relative to ITT are:<br>• 7 ineligible (4 prior surgical resections, 2 elevated CRP, 1 steroid use)<br>• 5 non-compliant due to receiving no Gem |
| | Gem | 35 | 28 | |
| | IMM-101 + Gem | 63 | 54 | |
| Safety | Total | 109 | n/a | All randomized patients who received at least one dose of the study drug |
| | Gem | 35 | | |
| | IMM-101 + Gem | 74 | | |

**Table 2: Patient Characteristics**

| | | Gem | IMM-101 + Gem |
|---|---|---|---|
| Age (years) | Median (range) | 66 (53 - 83) | 68 (45 - 88) |
| Gender | Male % | 60 | 51 |
| WHO performance status 0-1 | % | 91 | 83 |
| WHO performance status 2 | % | 9 | 17 |
| Time since diagnosis (months) | Median (range) | 0.8 (0.1 – 3.9) | 1.2 (0.1 – 6.9) |
| Completed study (12 cycles) | % | 3 | 16 |

## RESULTS

**Table 3: Median OS in the ITT and PP Sets**

| | Median OS | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ITT All | | ITT Metastatic | | PP All | | PP Metastatic | |
| | Months | n | Months | n | Months | n | Months | n |
| Gem | 5.6 | 35 | 4.4 | 28 | 5.6 | 35 | 4.4 | 28 |
| IMM-101 + Gem | 6.7 | 75 | 7.0 | 64 | 7.2 | 63 | 7.5 | 54 |
| % increase | 20% | | 59% | | 29% | | 70% | |
| Log rank test p value | p=0.075 | | p=0.010 | | p=0.022 | | p=0.002 | |

**Table 4: Median PFS in the ITT and PP Sets**

| | Median PFS | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ITT All | | ITT Metastatic | | PP All | | PP Metastatic | |
| | Months | n | Months | n | Months | n | Months | n |
| Gem | 2.4 | 35 | 2.3 | 28 | 2.4 | 35 | 2.3 | 28 |
| IMM-101+Gem | 4.1 | 75 | 4.4 | 64 | 4.4 | 63 | 4.4 | 54 |
| % increase | 71% | | 91% | | 83% | | 91% | |
| Log rank test p value | p=0.018 | | p=0.001 | | p=0.003 | | p<0.001 | |

**Figure 2: Overall Survival Kaplan–Meier Curves and % increase (inset) for ITT population, All Patients (A) and Metastatic Sub-group (B)**

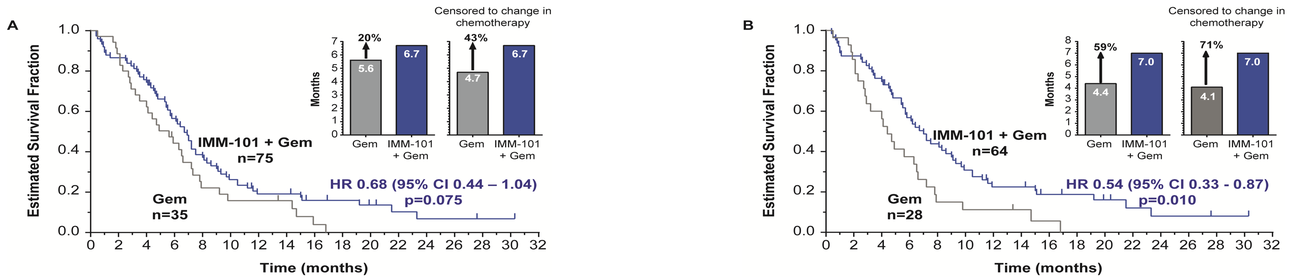



**Figure 3: Overall Survival Kaplan–Meier Curves and % increase (inset) for PP population, All Patients (A) and Metastatic Sub-group (B)**

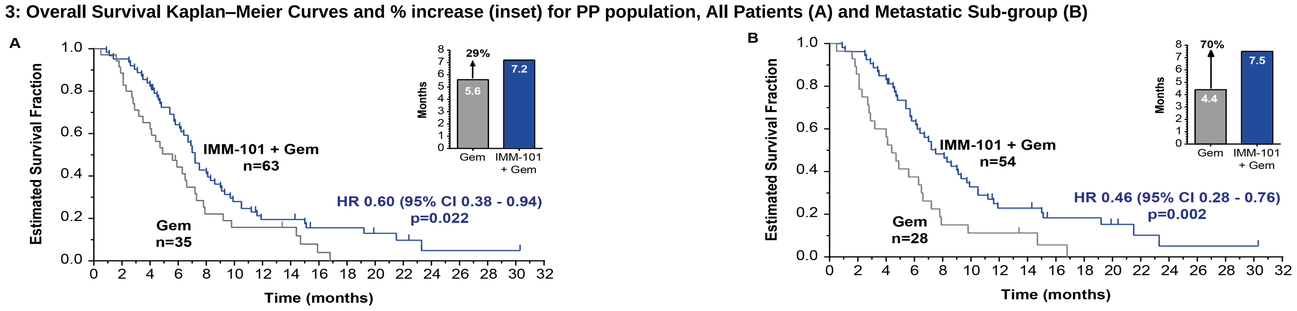
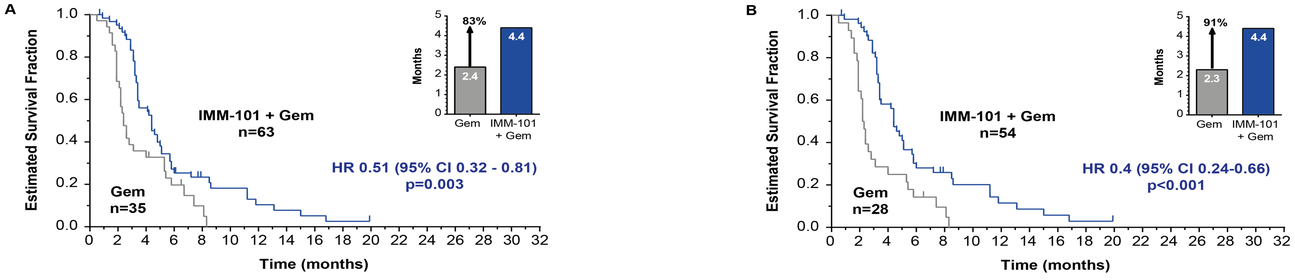



**Figure 4: Progression Free Survival Kaplan–Meier Curves and % increase (inset) for PP population, All Patients (A) and Metastatic Sub-group (B)**




## DISCUSSION

- In this randomized controlled clinical trial IMM-101, in combination with Gem, was associated with consistent and significant improvements in OS and PFS in pancreatic cancer patients in both the ITT and PP analysis sets.
- Improvements in OS and PFS were most notable in the predefined sub-group of patients with metastatic disease (84% of total).
- Twelve patients (16%) in the IMM-101 + Gem group completed the study (12 cycles) compared with 1 (3%) in the Gem group. This is reflected in the tail of the Kaplan-Meier curves, suggesting there may be more durable responses in a proportion of patients, the explanation for which is the subject of ongoing biomarker research.
- Patients with locally advanced disease at the time of enrolment were eligible for the study and 18 such patients were included, 11 randomized to IMM + Gem and 7 to Gem. This sub-group was too small to draw firm conclusions but there was no evidence for a beneficial effect of IMM-101, which is consistent with findings from preclinical studies that indicated a more profound effect of IMM-101 on metastases than on the primary tumor (Elia *et al.*, 2013; Fowler *et al.,* 2014).
- IMM-101 does not appear to confer an incremental safety burden beyond that associated with chemotherapy and the disease itself.
- This randomized, controlled, proof of concept study has exceeded its objectives, providing clear direction for the further development of IMM-101 in combination with chemotherapy as a first line treatment option for metastatic pancreatic cancer.

## SAFETY

**Table 5: Exposure Summary**

| | Gem | IMM-101 + Gem |
|---|---|---|
| Days of exposure to IMM-101 median (range) | n/a | 113.5 (1-344) |
| Days of exposure to Gem median (range) | 59 (8-246) | 78 (1-337) |

**Table 6: Grade 3 or Higher Adverse Events (≥ 5%)**

| Adverse Event | Gem n (%) | IMM-101 + Gem n (%) |
|---|---|---|
| Neutropenia | 7 (20.0) | 15 (20.3) |
| Asthenia | 2 (5.8) | 8 (10.8) |
| Abdominal Pain | 1 (2.9) | 6 (8.1) |
| Anemia | 1 (2.9) | 6 (8.1) |
| Disease Progression | 3 (8.6) | 3 (4.1) |
| ALT increased | 2 (5.7) | 3 (4.1) |
| Thrombocytopenia | 3 (8.6) | 4 (5.5) |
| Leukopenia | 4 (11.4) | 4 (5.5) |

## CONCLUSION

- Clinically meaningful increases in OS and PFS were demonstrated with IMM-101.
- No additional burden of adverse events above those relating to chemotherapy or the underlying disease was observed.

## REFERENCES

Elia A *et al*., 2013. J Immunother Cancer 1: Sup 1, P215

Stebbing J *et al*., 2012. Ann Oncol 23:1314

Fowler D *et al*., 2014 J Immunother Cancer *in press*

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