**IMAGE 1** (Immune Modulation and Gemcitabine Evaluation), a Randomised, Open-label Phase II Trial Comparing Gemcitabine with and without IMM-101 in Advanced Pancreatic Cancer (including results from the long-term follow-up Sub-Study)

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**Survival in advanced pancreatic cancer**

- The introduction of nab-paclitaxel gemcitabine and FOLFIRINOX has improved median survival for patients with metastatic disease and good performance status (PS, ECOG 0-1) (8.7 months) and 11.1 months respectively of the 12 to 30 studied with and without IMM-101 in subjects with uncontrolled (uncontrolled stage 3 or stage 4) pancreatic cancer\(^1\).
- Patients randomised 2:1 to IMM-101 (0.1mg/mL, Intravenous) + GEM (1000mg/m\(^2\)) or GEM
- Study treatment could be continued to a maximum of 12 cycles of GEM in the Main Study.
- Patients from both treatment groups who completed the Main Study were eligible to participate in a long-term follow-up study (Sub Study) where all received IMM-101 and, at the Investigator’s discretion, adjuvantive chemotherapy.
- Efficacy was assessed with Kaplan-Meier survival curves and log-rank test.
- All statistical testing was at 2-sided 5% significance level with hazard ratios and p-values from Cox regression models.

**The IMAGE 1 Trial**

**Patients**

- **ITT (All Patients)**
- Open-label phase 2 study (NCT01303172) comparing safety and efficacy of IMM-101 with and without GEM (monotherapy) in subjects with advanced, resected or locally advanced, metastatic pancreatic cancer.
- Conclusions from the completed IMAGE 1 Sub-Study:
  - The survival benefit of IMM-101 demonstrated in the IMAGE 1 Study is maintained over a longer period of follow-up.
  - The survival benefit of IMM-101 in terms of median OS in the IMAGE 1 Trial (11.0 months) is improved over the results from the FOLFIRINOX arm of the MPACT trial (7.3 months).
  - In the IMAGE 1 Sub-Study, the median OS in the IMM-101 group was 14.6 months, which was consistent with the results from the IMAGE 1 Study (11.0 months).

**The Investigational Product: IMM-101**

- **Patients**
- Administered by intradermal injection to the upper arm, alternate arms for each dose.
- Myeloid dendritic cell (DC) activator, enhancing antigen processing.
- Produces Type-1 immune response, with formation and activation of CD8+ T lymphocytes (CTLs) and increased production of the cytokine interferon-gamma (IFN-γ).
- Matures monocytes into Type-1 macrophages (M1) and increases the number of activated IFN-γ producing Th1, NK, Vβ-T and NKT cells.
- CTLs, M1, NK, Vβ-T cells and NKT cells and IFN-\(\gamma\) are known to play crucial roles in anti-tumour responses, attacking the tumour through different but complementary pathways.

**Frequently Asked Questions**

- The results indicate a benefit for the IMM-101 + GEM group but the median OS values are low compared to other studies – why?
  - Median OS for the IMM-101 + GEM group is similar to results from other studies for patients randomised to GEM (e.g. ariprazol trial). OS in trials of metastatic patients can vary depending on demographics and was only 4.3 months for patients with Karmalka 70-80 (ECOG 1) in the MPACT trial. Phase 3 trials usually limit recruitment to newly diagnosed patients, whereas IMM-101 had no limit to the time from diagnosis (All ITT patients 0.1-6.9 months for IMM-101 + GEM group; 0.1-3.9 for GEM).
- Do you think any imbalance in baseline patient characteristics could account for the survival differences?
  - Explanatory univariate analyses (Cox PH regression models) showed the HR to be maintained when factors of CA19-9, E CD4, LDH, NLR, total bilirubin, age and PS were accounted for, indicating baseline factors were not responsible. Explanatory multivariate stepwise Cox PH regression analyses supported this conclusion\(^8,9\).
- How do the long-term survival prediction figures compare with those from other studies?
  - Long-term survival from the MPACT study showed 10% survival probability at 24 months and 4% at 36 months for the nab-paclitaxel/GEM group, with 5% at 24 months and 0% at 36 months for the GEM group\(^1\). IMM-101 results compare favourably as it should be borne in mind that IMM-101 was a proof of concept study and genuine treatment differences were not planned to be detected with high power.
  - Which immunotherapies in the Sub-Study receive?
  - Eight of the 12 patients took chemotherapy with carboplatin (the most frequently used 5 patients). Others were GEM (paclitaxel, 3 patients), GEM and paclitaxel alone (2 patients) and combinations or sole use of oxaliplatin, 5-fluorouracil and irinotecan (3 patients). The number of different immunotherapies ranged from 1 to 4.
- How could these have influenced your results?
  - Long-term survival rates are usually influenced by subsequent therapy, taken after study, with 38-50% second line therapy used in treatment arms of recent phase 3 trials\(^10\). However, for IMM-101, patients continued on study so they could still receive IMM-101.

**Safety and Tolerability**

- **Overall Survival Results**
  - **ITT (All Patients)**
  - **ITT Metastatic Subgroup**
  - **Complete Kaplan-Meier survival curves with log-rank test for comparison of overall survival (OS) and 2-sided 5% significance level with hazard ratios and p-values from Cox regression models.

**Conclusions from the completed IMAGE 1 Sub-Study:**

- **The IMAGE 1 Sub-Study identified long-term survivors from the Main Study and showed IMM-101 to be well tolerated over an extended period, with a maximum exposure of 46.5 months.**
- **The survival probability at 24, 30 and 36 months indicated long-term benefits of the previously reported survival benefit of IMM-101 with GEM and, in some cases, with a variety of other anti-cancer treatments.**
- **No additional safety signals were identifiable for IMM-101.**

**Future Directions:**

- **IMAGE 1 demonstrated promising efficacy and tolerability of IMM-101 + GEM with the possibility of long-term use and survival benefits.** There is potential for use in metastatic pancreatic cancer as:
  - First line treatment in patients who are unsuitable for more aggressive regimens.
  - Second-line/maintenance therapy.

**References**


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