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# Immodulon Therapeutics

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## IMM-101

A Systemic Immunomodulator being  
Developed for Cancer Indications

### Introduction

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## Why is IMM-101 of interest?

- **Multi-modal systemic immunomodulator** containing heat killed *Mycobacterium obuense* (NCTC 13365) that can help restore effective anti-tumour immune function.
- **A hierarchy of clinical data suggests broad clinical applicability.** In a randomised Phase 2 pancreatic cancer study, up to 70% increase in median overall survival when added to gemcitabine; 33% 5 year survival in Stage IIIb – IV melanoma; compassionate use cases indicate potential activity in sarcoma, ovarian, uterine and prostate cancers.
- **Safety and tolerability.** Minimal additional safety burden.
- **Regulatory pathway clarity.** Formal and clear guidance on regulatory pathway from EMA and FDA; orphan drug status in EU and US.
- **In-house manufacturing** with scalable process, IP, know-how.
- **Collaborative approaches** allow more therapeutic options, including novel combinations to be evaluated in parallel with Immodulon's core pancreatic cancer work.



## Immodulon

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- UK-based and incorporated, formed in 2007, backed solely by private investment
- Focused on cancer immunotherapy and the role of heat-killed mycobacteria as therapeutically useful systemic immunomodulators
- Clinically led with experienced management team, all with pharmaceutical and biotech industry backgrounds
- Goal of demonstrating *proof of concept* for lead product, IMM-101, in one cancer indication of significant medical need has been met
- Parallel investment in manufacturing has provided scalable and commercially viable processes for drug substance and drug product



## Why Collaborative Approaches are of Interest?

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- **Additional expertise:**
  - Therapeutic area
  - Scientific knowledge
  - Biomarker research to aid patient selection and treatment efficiency
- **Additional product and indication options**
  - Enhanced access to novel combinations
  - Earlier access for patients if successful
- **Resource:**
  - Co-operation with leading clinical researchers
  - Increased capacity to exploit broad therapeutic potential of IMM-101
  - Enhanced commercial knowledge and capability

**Experienced, committed and knowledgeable Immodulon team complemented by investigator-initiated research**



## Why Pancreatic Cancer as Initial Indication?

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- Lack of effective alternative treatments
- Orphan indication benefits
- Short life expectancy so overall survival a realistic, achievable and objective measure of efficacy for proof-of-concept trial
- IMM-101 has the potential to extend survival horizon while preserving quality of life
- Randomised Phase 2 data constitute firmest available evidence base

**A hierarchy of evidence suggests activity across a range of tumour types**



## Mutual Benefits

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### For Immodulon

- Parallel clinical development in different indications and with novel combinations
- Increased depth of expertise to enhance development strategy
- Potential resource synergies

### For Collaborator

- Access to novel immunotherapeutic with attractive safety profile
- IMM-101 ideally suited for combination use
- Unique MoA with potential for broad clinical utility
- Proof of concept established in randomised Phase II clinical trial



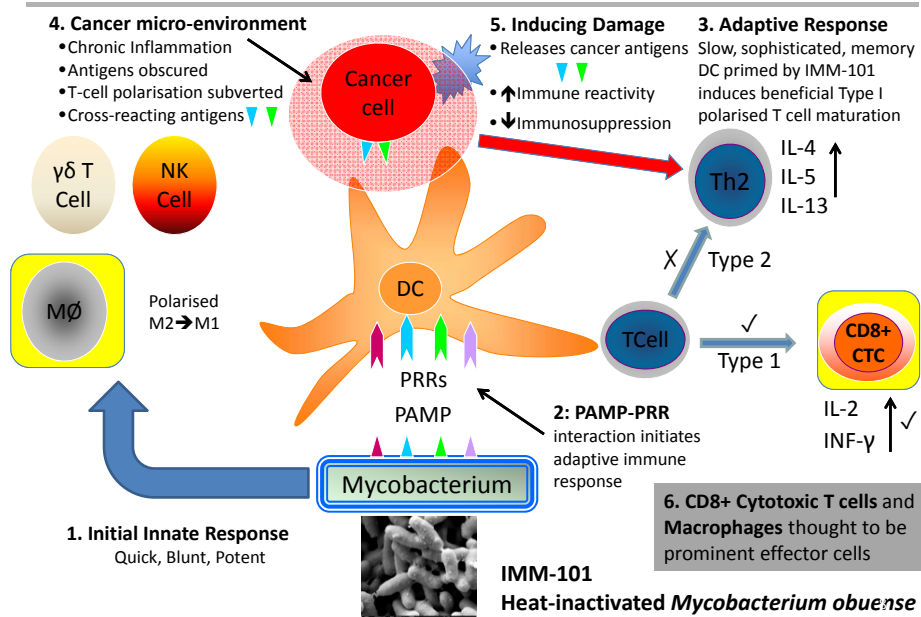
## IMM-101: Suspension of Heat Killed *Mycobacterium obuense* (NCTC13365) for Intradermal Injection

- Produced by fermentation, inactivated by autoclaving and aseptically filled into single use vials
- Standard dose 0.1mL of 10mg/mL suspension injected intradermally to the upper arm
- Safe and well tolerated
- Local effects at injection site occur with variable intensity but are easily managed



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## IMM-101: Multi-faceted but Directed Mechanism of Action



## **IMM-101: Proposed Mechanism of Action**

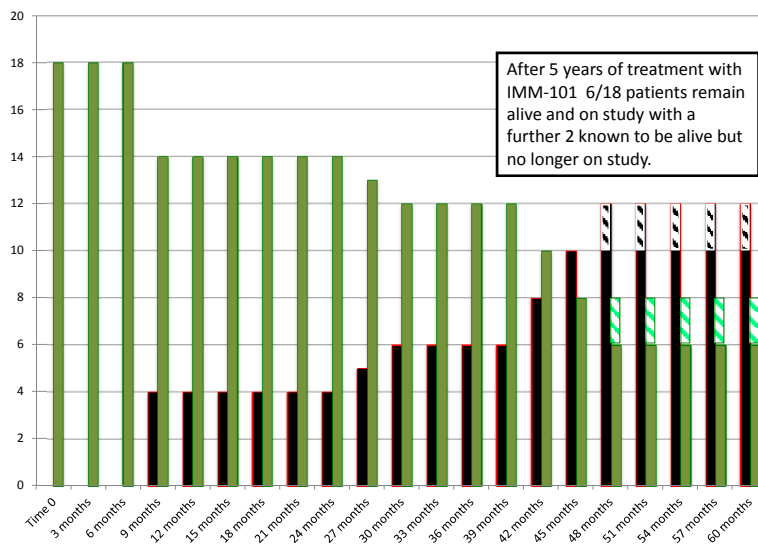
1. Initial response involves the innate immune system with activation and polarisation (M2→M1) of macrophages via precursor monocytes, natural killer cells and  $\gamma\delta$  T-cells.
2. Mycobacterial cell walls have multiple antigens - protein, carbohydrate and lipid - forming what has become known as the Pathogen Associated Molecular Pattern (PAMP). The PAMP interacts with pattern recognition receptors (PRR), specifically TLRs 2 and 6 and possibly others, on dendritic cells following intradermal injection of IMM-101. Intradermal delivery is important as the skin is one of the regions with a high concentration of dendritic cells.
3. This 'directs' the adaptive immune response through T-cell maturation into different effector phenotypes, characterised by cytokine profiles. It seems only a few mycobacteria are able to elicit the optimal immunomodulatory response
  - Up-regulation of T-helper 1 (Th1) pathway with enhanced production of IL-2 and Interferon- $\gamma$ , which together with the innate effects is termed a 'Type 1 immune response'
  - Down-regulation of T-helper 2 (Th2) characterised by cytokines like IL-4, IL-5 and IL-13 (Type 2)IMM-101 does this, and increases the number of functional CD8+ cytotoxic T-cells.
4. Cancer cells also have multiple surface antigens and there is evidence that some may cross-react with those expressed by mycobacteria. However, cancer cells, by creating an inflammatory microenvironment, 'hide' from the immune system by obscuring these surface antigens. The immunosuppressive tumour microenvironment also subverts T-cell polarisation towards the undesirable Th2-biased profile, but IMM-101 can down-regulate this Th2 response.
5. Causing damage by chemical or physical means may bring further benefits by disrupting the tumour infrastructure so that antigens are more 'visible'. Specific synergies are postulated with drugs such as gemcitabine, paclitaxel (both of which inhibit myeloid derived suppressor cells) and cyclophosphamide, which has a similar effect on tolerogenic regulatory T-cells.
6. The emerging evidence is that CD8+ T cells and macrophages may be key effectors 'driven' by IMM-101 (as highlighted) but other cells and pathways may also be involved.

## **IMM-101-001: First in Human Study (Stage IIIb,c and Stage IV Melanoma Patients)**

**An intra-patient placebo-controlled, Phase I clinical study, to evaluate the safety and tolerability of intra-dermal IMM-101 (heat-killed Mycobacterium obuense) in adult melanoma cancer patients**

- 18 patients - 3 stage IIIb, 3 stage IIIc and 12 stage IV
- 3 sequentially dosed cohorts, 2 week dose interval, total of 3 doses  
0.1mg, 0.5mg or 1mg IMM-101
- Results published:  
Stebbing, J et al. [Ann Oncol. 2012 May;23\(5\):1314-9](#)
- Named patient programme initiated
- Long term follow-up trial (IMM-101-008) - safety and survival

## Encouraging Survival in Stage IIIb,c/IV Melanoma



An intra-patient placebo-controlled phase I trial to evaluate the safety and tolerability of intradermal IMM-101 in melanoma  
 Stebbing, J et al. *Ann Oncol.* 2012 May;23(5):1314-9 (Trial began March 2010)

## IMAGE 1

### Immune Modulation And Gemcitabine Evaluation

**IMM-101 Extends Survival and Maintains Quality of Life in IMAGE 1, a Randomised, Open-Label, Phase II Trial Comparing Gemcitabine with and without IMM-101 in Advanced Pancreatic Cancer**

ORAL PRESENTATION AT ESMO WORLD CONGRESS ON GASTROINTESTINAL CANCER, 1 JULY 2015

Angus G. Dalglish<sup>1</sup> and the IMAGE 1 Trial Investigators<sup>2</sup>

<sup>1</sup>St George's, University of London

<sup>2</sup>See Acknowledgements Slide

## Background

### Pancreatic Cancer - Goals of Patients and Caregivers

- Maintain quality of life (QoL)
- Extend survival
- Manage symptoms

### IMM-101

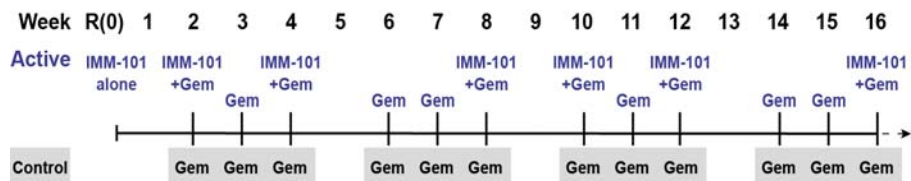
- Suspension of heat-killed *Mycobacterium obuense* (NCTC 13365)
- Systemic immunomodulator administered by intradermal injection
- Induces CD8+ T cell responses, reduces metastatic burden in mouse models

### IMAGE 1

- Clinically significant increases in OS and PFS
- Survival curve shape characteristic of immunotherapy
- No incremental toxicity or immune-related toxicities

## Methods

- Phase II trial devised in 2010 when mainstay of treatment in EU and US was gemcitabine
- 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<sup>2</sup>) or Gem alone according to the schedule shown on the next slide.
- Per protocol this could be continued to a 12-cycle maximum.



## Analysis Sets and Sub-groups (Patient Numbers)

Set		All	Metastatic	Composition
ITT	Total	110	92	All randomized patients
	IMM-101 treated	75	64	
	Control	35	28	
PP	<b>Total</b>	<b>98</b>	<b>82</b>	<b>Exclusions relative to ITT are:</b> <ul style="list-style-type: none"> <li>• 7 ineligible (4 prior surgical resections, 2 elevated CRP, 1 steroid use)</li> <li>• 5 non-compliant due to receiving no Gem</li> </ul>
	<b>IMM-101 treated</b>	<b>63</b>	<b>54</b>	
	<b>Control</b>	<b>35</b>	<b>28</b>	
Safety	Total	109	n/a	All randomized patients who received at least one dose of the study drug
	IMM-101 treated	74		
	Control	35		



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## Patient Characteristics

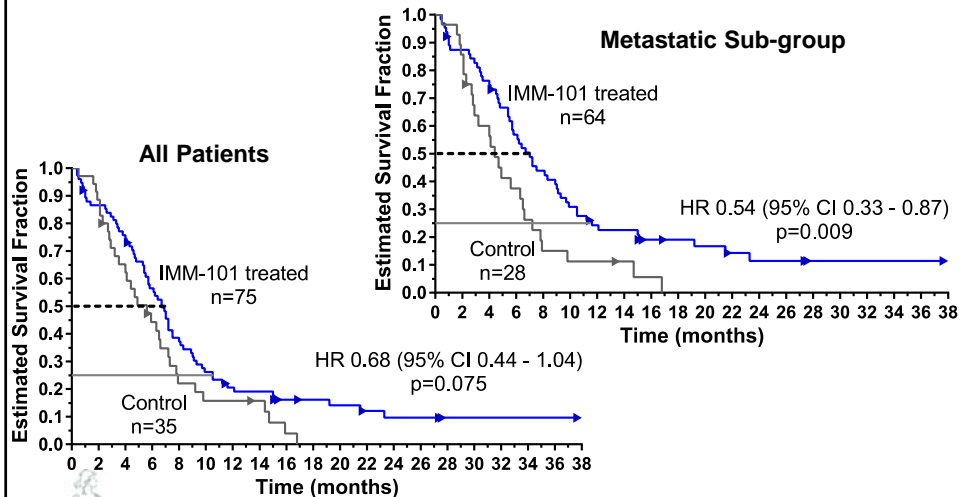
		IMM-101 treated	Control
Age (years)	Median (range)	68 (45 - 88)	66 (53-83)
<b>Age &lt; 65</b>	<b>%</b>	<b>33</b>	<b>34</b>
Age ≥ 65	%	67	66
<b>Gender</b>	<b>Male %</b>	<b>51</b>	<b>60</b>
WHO performance status 0-1	%	83	91
WHO performance status 2	<b>%</b>	<b>17</b>	<b>9</b>
Time since diagnosis (months)	Median (range)	1.2 (0.1 – 6.9)	0.8 (0.1 – 3.9)
<b>Completed study (12 cycles)</b>	<b>n (%)</b>	<b>12 (16)</b>	<b>1 (3)</b>



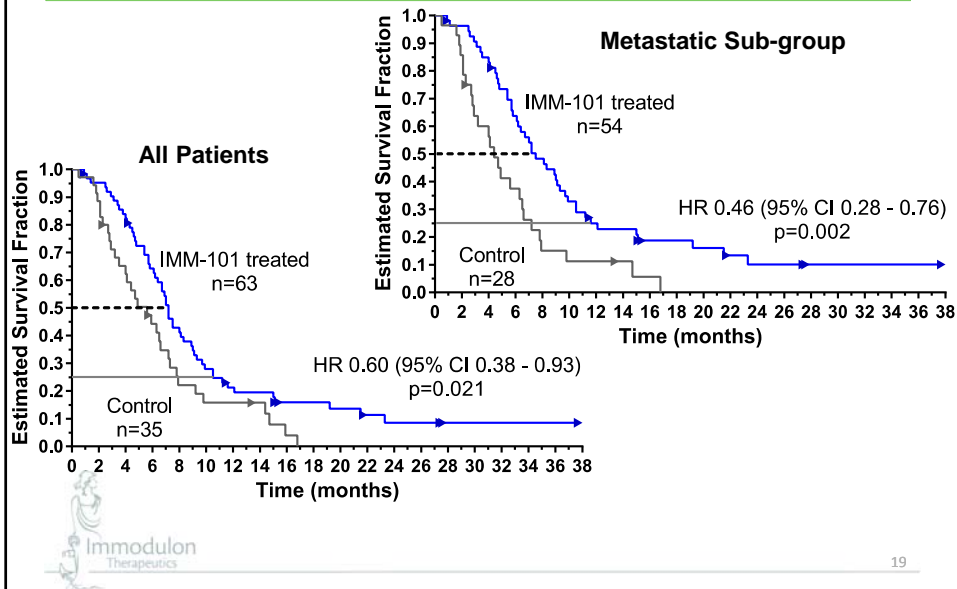
## Overall Survival and Progression Free Survival

	Median OS (months)		Median PFS (months)	
	ITT All	ITT Metastatic	ITT All	ITT Metastatic
<b>IMM-101 Treated</b>	<b>6.7</b>	<b>7.0</b>	<b>4.1</b>	<b>4.4</b>
Control	5.6	4.4	2.4	2.3
% increase	20%	59%	71%	91%
Log rank p value	0.072	0.009	0.016	0.001

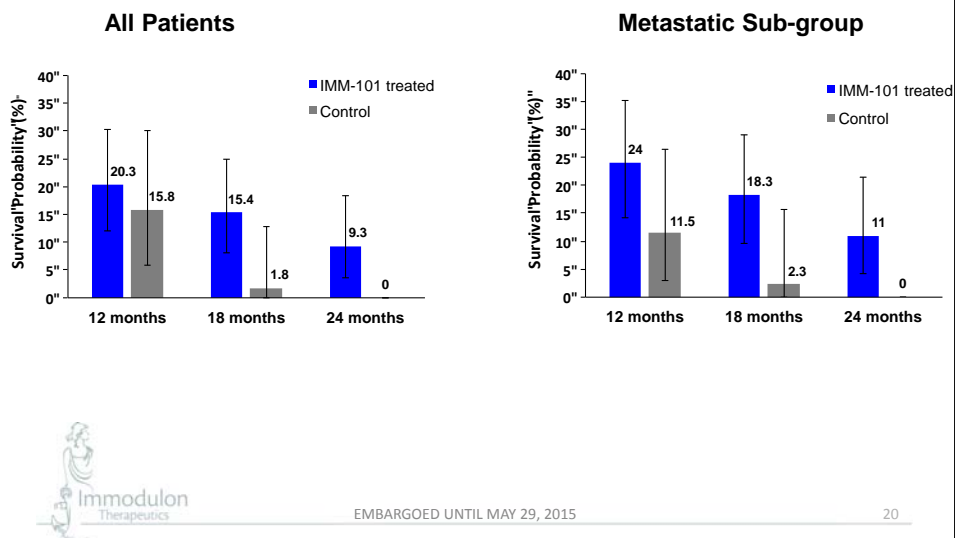
## Overall Survival Kaplan- Meier Curves ITT Population



## Overall Survival Kaplan- Meier Curves PP Population



## Survival Probability at 12, 18 and 24 months: ITT population



## Times Corresponding to 25% Survival Probability

Time Corresponding to 25% Survival Probability (months)		
ITT All	IMM-101 treated	10.5
	Control	7.9
ITT Metastatic	IMM-101 treated	11.6
	Control	7.2

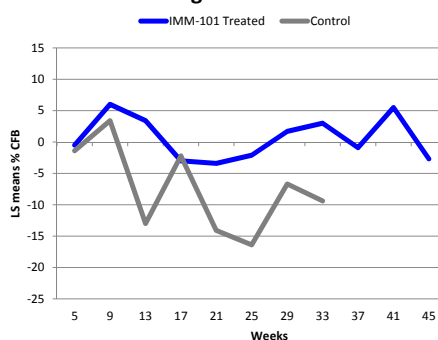


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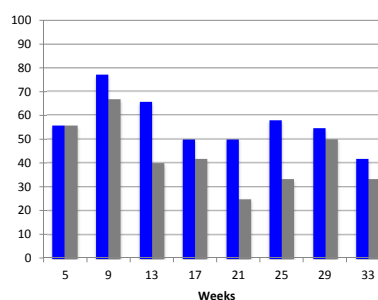
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## Quality of Life QLQ-C30 Global Health Status

LS Means Change from Baseline



% Patients with Stable or Increased GHS from Baseline



IMM-101 Treated	45	39	32	24	20	19	11	12	10	10	9
Control	27	18	15	12	8	6	4	3	2	1	1

Number of patients completing QLQ-C30 Global Health Status

## Safety and Exposure Summary

	IMM-101 Treated (n=74)	Control (n=35)
Total number of AEs	1264	477
Mean time on study	5.52 months	3.80 months
AEs per month on study	3.05	3.59
Mean exposure to gemcitabine	118.7 days	90.5 days
AEs per month of gemcitabine	4.37	4.59

## Safety - Grade 3 and Higher Adverse Events (≥ 5% incidence in either group, to 12 cycles)

Adverse Event (preferred term)	IMM-101 treated n (%)	Control n (%)	Incidence Rate Difference (IMM-101treated – Control)
Asthenia	8 (11)	1 (3)	8%
Abdominal Pain	6 (8)	1 (3)	5%
Vomiting	4 (5)	0	5%
Anemia	6 (8)	1 (3)	5%
Biliary sepsis	4 (5)	0	5%
Bile duct obstruction	4 (5)	1 (3)	2%
Neutropenia and/or neutrophil count decreased	13 (18)	6 (17)	1%
Leukopenia and/or WBC count decreased	3 (4)	4 (11)	-7%
Hypokalemia and/or blood potassium decreased	0	2 (6)	-6%
Fatigue	4 (5)	4 (11)	-6%
Urinary tract infection	1 (1)	2 (6)	-5%
Disease Progression	3 (4)	3 (9)	-5%
Thrombocytopenia and/or platelet count decreased	5 (7)	3 (9)	-2%
ALT increased	3 (4)	2 (6)	-2%

## Conclusions

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- Clinically meaningful increases in OS in IMM-101 treated patients, notably in pre-defined sub-group of patients with metastatic disease (84% of total).
- Overall shape of IMM-101 Kaplan-Meier curves characteristic of immunotherapy agents (McDermott et al., 2014)
- Continued separation of the Kaplan-Meier curves to 24 months and survival probabilities at 12, 18 and 24 months are indicative of a durable response in some patients – chemotherapy curves tend to converge
- Quality of life maintained with indications of improvements in some scores.
- No additional burden of adverse events in IMM-101 treated patients above that relating to chemotherapy or the underlying disease and no pattern of immune-related toxicities.
- First positive study of an immunotherapy/chemotherapy combination given **first line** in PDAC
- Combination of IMM-101 with additional immunotherapies such as checkpoint inhibitors logical and also of interest.



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## Future Plans

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- To continue development of IMM-101 in pancreatic cancer

Immodulon priority

- To investigate IMM-101 in alternative cancer indications

Proof of concept trials in other cancers, possibly investigator led

- To establish potential of novel and logical combinations

CRUK/ECMC Combinations Alliance



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## IMM-101 Combinations Under Consideration

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### General concepts:

Immunotherapy combinations to potentiate overall effect  
Combination with drugs reported to have beneficial immune effects  
Chemotherapy or radiotherapy combinations

### Specific ideas:

- Checkpoint blockade Anti-CTLA-4/PD1/PD-L1  
remove the brakes but apply some steering
- Low dose cyclophosphamide conditioning  
inhibit Tregs
- Other low dose cytotoxic chemotherapy or targeted radiotherapy  
damage tumour, release tumour-associated antigens
- Alternating chemotherapy with IMM-101 immunotherapy 'backbone'

