LAG-3: Identification & Validation Of Next Generation Checkpoint Pathways

ICI Europe Conference

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Bad-Hombourg, Germany

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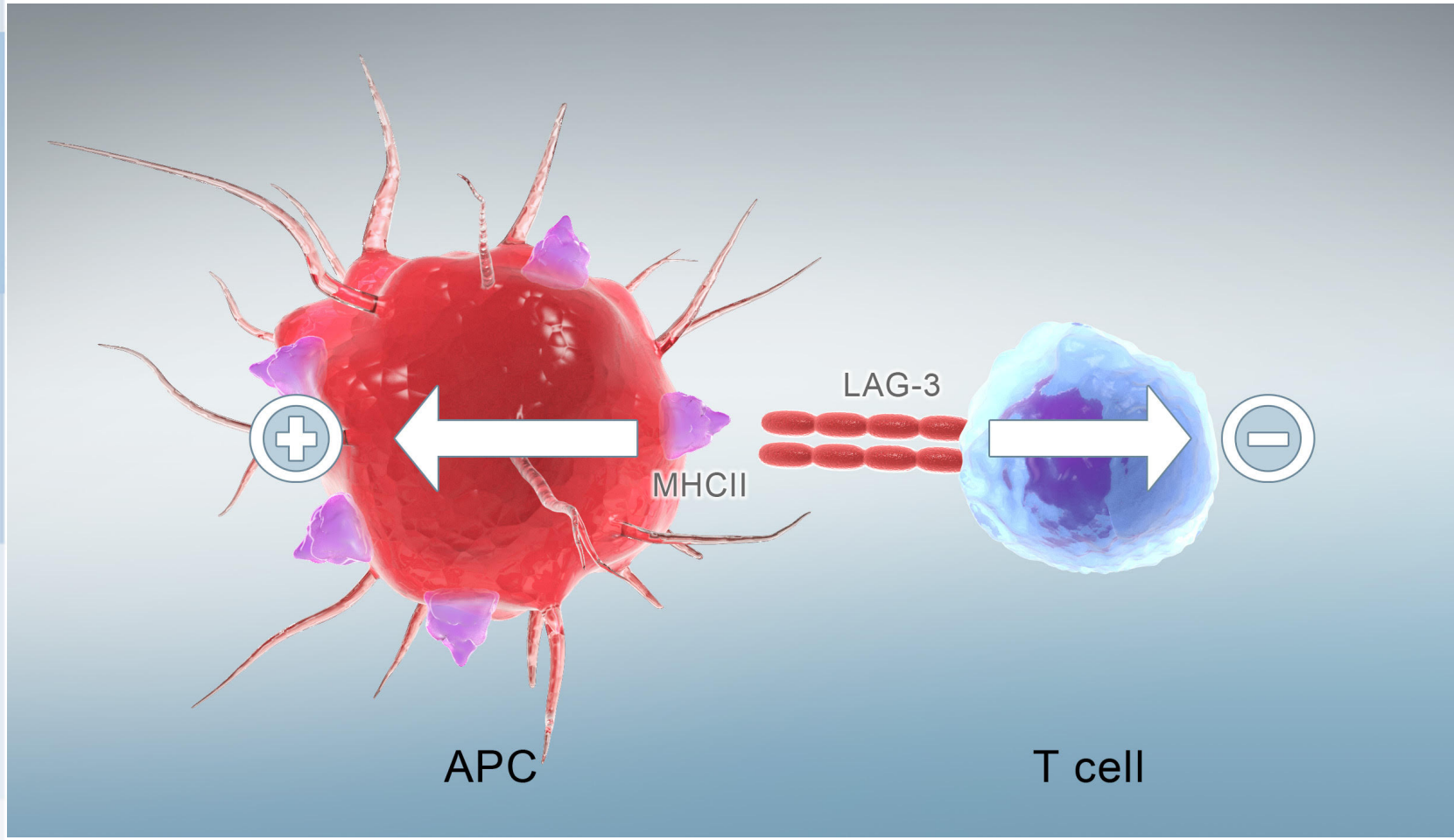
ASX:PRR; NASDAQ:PBMD

LAG-3/MHC class II interaction



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First-in class APC Activator

IMP321 (LAG-3Ig)

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IMP321

- A soluble dimeric recombinant form of LAG-3 for the **activation of the APC* network in the body**
- Very stable human protein with **high affinity for dendritic cells/monocytes (i.e. APC)**
- Effectively tested **as chemoimmunotherapy** in several indications
- Extension to other indications possible by coupling with other first-line chemotherapy
- Can also be used at low doses as an **adjuvant to cancer vaccines**

*APC = Antigen Presenting Cell

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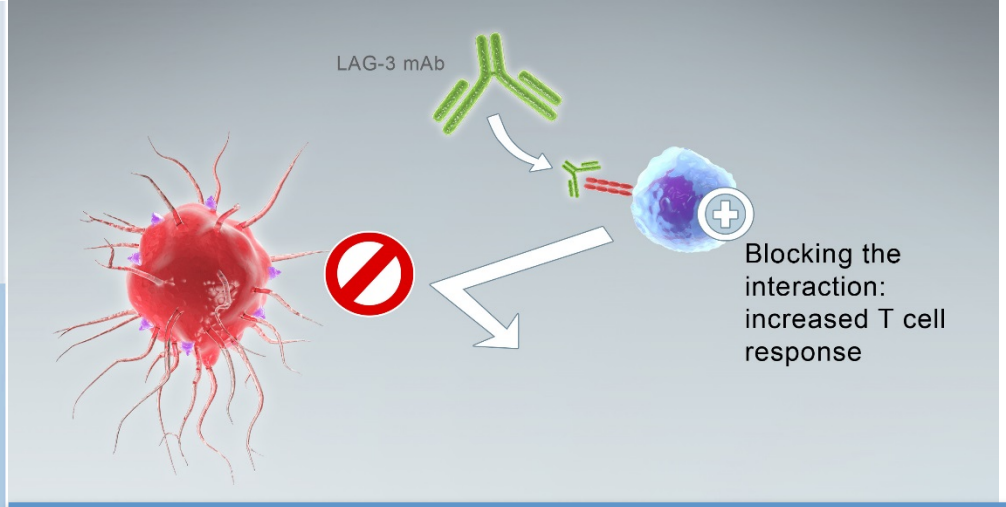
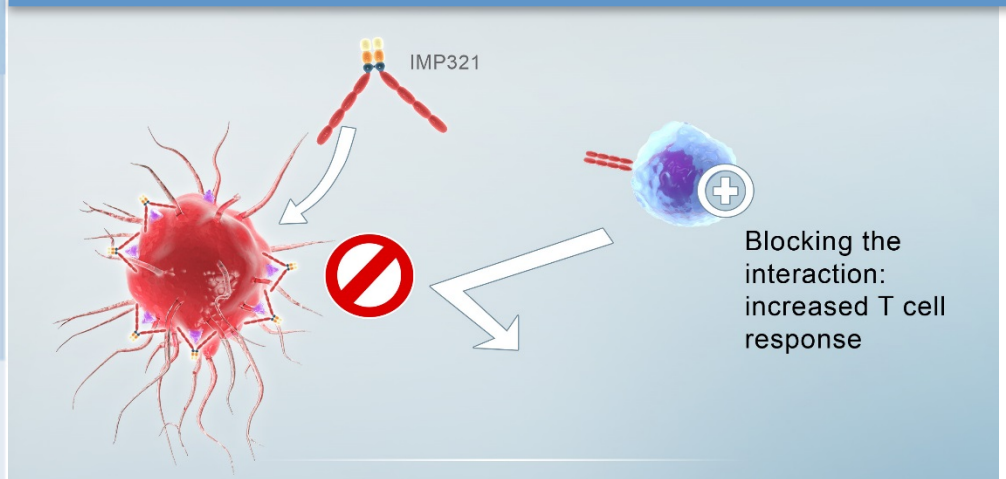
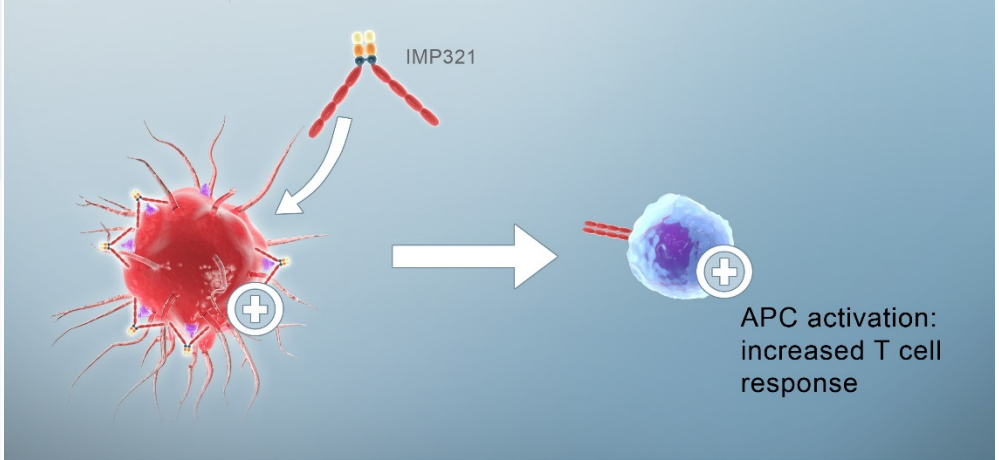


LAG-3 blocking mAb:
the typical immune checkpoint inhibitor



IMP321:
the atypical immune checkpoint inhibitor



IMP321:
the APC activator
(primary MoA)

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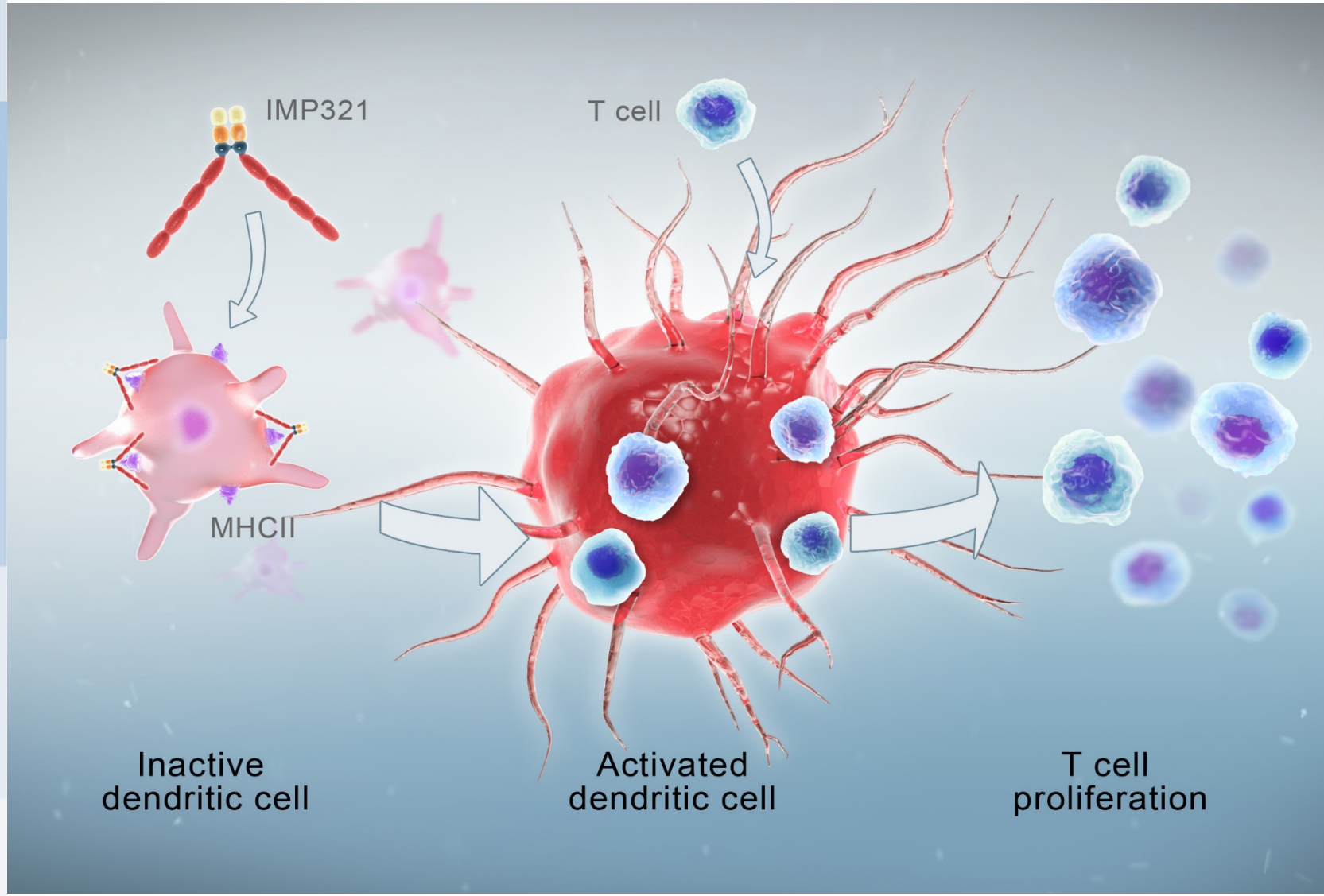
IMP321: a first-in-class APC activator



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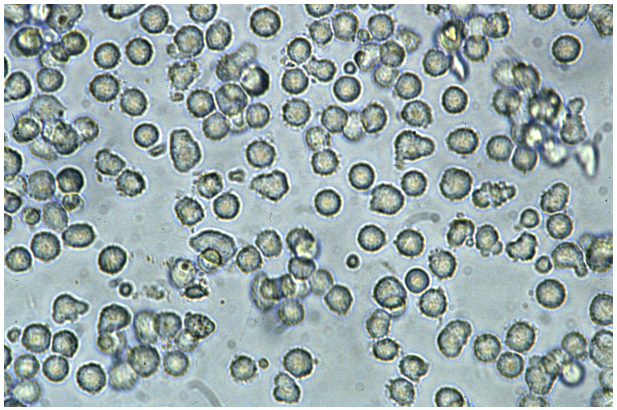
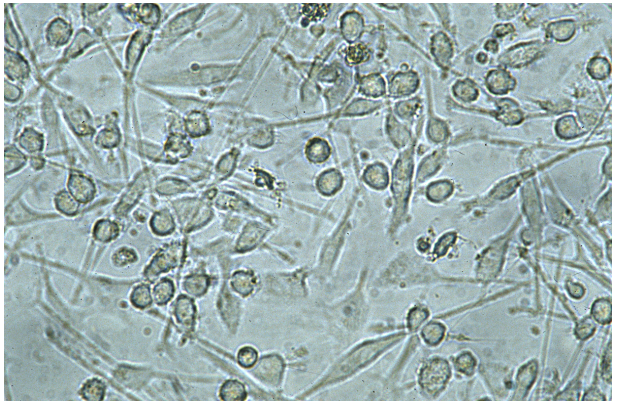
IMP321 as an MHC class II agonist
(primary MoA)

mDC + hIgG1 (negative control), 4 hrs



mDC + 1 µg/ml LAG-3Ig, 4 hrs



Monocyte-derived DC (mDC): human blood monocytes are cultured with GM-CSF + IL-4 for 5 days and are differentiated into immature DC

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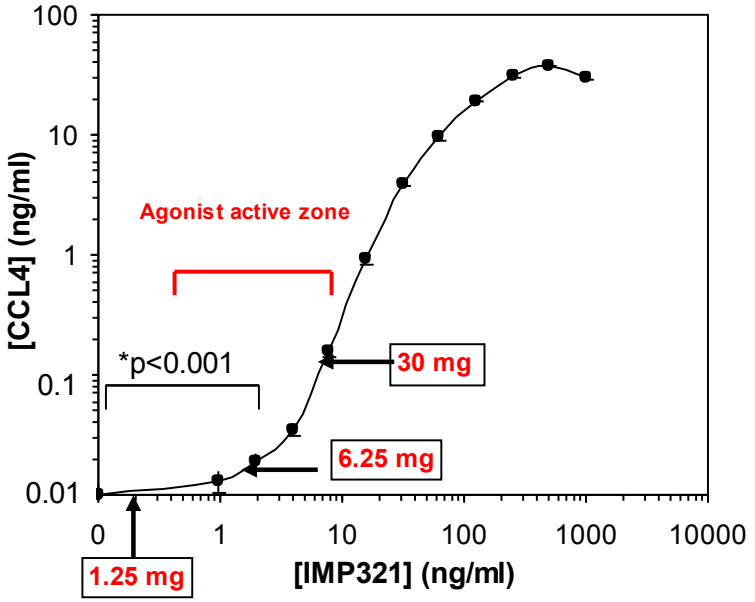
IMP321 as an MHC class II agonist

In vitro bioactivity of IMP321. IMP321 potency to induce CCL4 (MIP-1β) secretion was tested using the MHC class II$^+$ human monocytic THP-1 cells. The results are presented as concentration of CCL4 produced in supernatant after 4 hrs of culture (mean of 5-plicate determinations ± SD) as a function of IMP321 concentration on a logarithmic scale. The lowest concentration of IMP321 inducing a response statistically different from the baseline is indicated. The concentrations found in the serum 2hr after s.c. injection of 1.25, 6.25 and 30 mg in patients are indicated by arrows.



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IMP321 Clinical Trials Overview

Protocol	Patient Population	Compound	Status
P001 Phase I	healthy males	IMP321 (adjuvant)	Completed
P002 Phase I	healthy males	IMP321 (adjuvant)	Completed
P003 Phase I	metastatic renal cell carcinoma	IMP321 (monotherapy)	Completed
P005 Phase I	metastatic breast carcinoma	IMP321 (chemo-immunotherapy)	Completed
P006 Phase I/IIa	disease free melanoma	IMP321 (adjuvant)	Completed
P007 Phase I/IIa	metastatic melanoma	IMP321 (adjuvant)	Completed
P008 Phase I/II	advanced pancreatic cancer	IMP321 (chemo-immunotherapy)	Completed
P009 Phase I/IIa	melanoma	IMP321 (adjuvant)	Completed
P010 Phase II	prostate carcinoma	IMP321 (adjuvant)	Completed

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Two Key Concepts

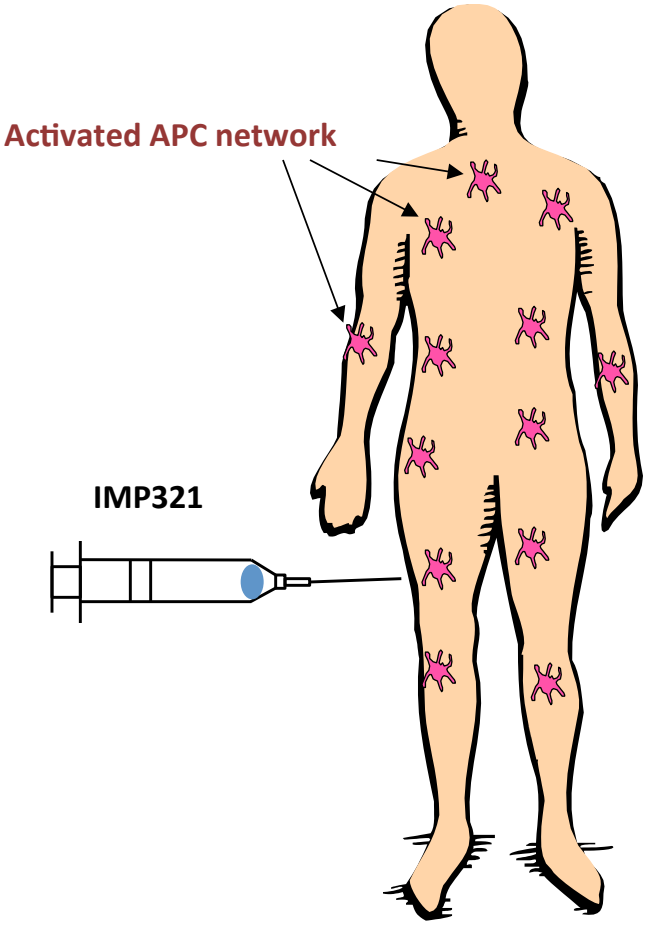
"APC Activators" and "Chemo-immunotherapy"

APC activators

- APC activators boost the activation of the APC network in the body
- Resulting in a more powerful anti-tumor immune response

Chemo-immunotherapy

- Chemo-immunotherapy is the administration of an immunostimulant the day after chemotherapy
- Tumour debris released following chemotherapy is captured, digested by APC and then presented to the immune system



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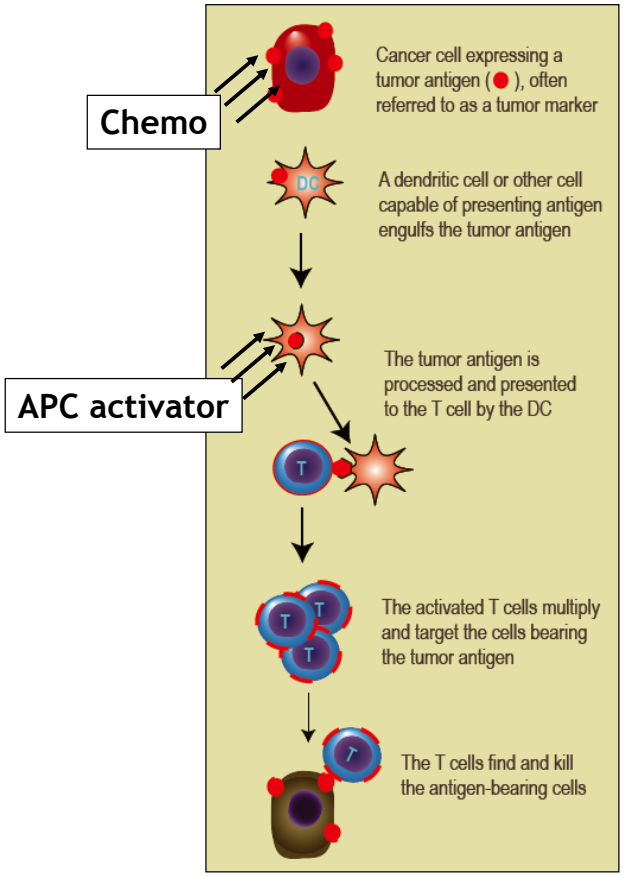
A new field: combination of chemo with a non-specific (i.e. not a vaccine) active immunotherapy

An APC activator like IMP321 given after chemotherapy induces the APCs to mature and transport the apoptotic cell death tumor antigenic debris to the lymph nodes for presentation to the T cells. Importantly, a concentration of only a few ng/mL of IMP321 has been shown to be active *in vitro* on APCs, showing the great potency of IMP321 as an agonist of the immune system.



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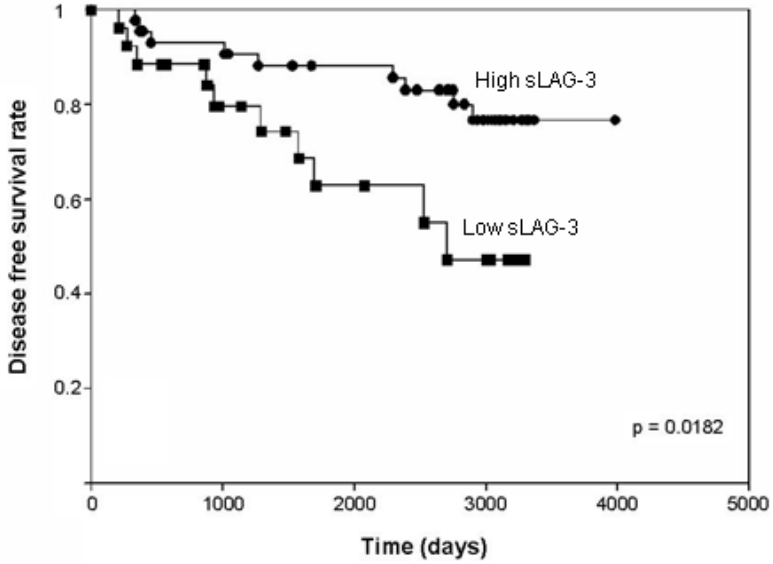
Pre-treatment serum sLAG-3 concentration predicts survival in breast cancer

Survival analysis of patients with breast carcinoma according to pre-treatment serum sLAG-3 concentration. The Kaplan–Meier curves for the duration of disease-free survival according to the concentration level of natural sLAG-3 found in the serum at time of first diagnosis are shown for progesterone receptor positive tumor patients.
Low sLAG-3 (<120 pg/ml), n=26;
High sLAG-3(> 120 pg/ml), n=43.



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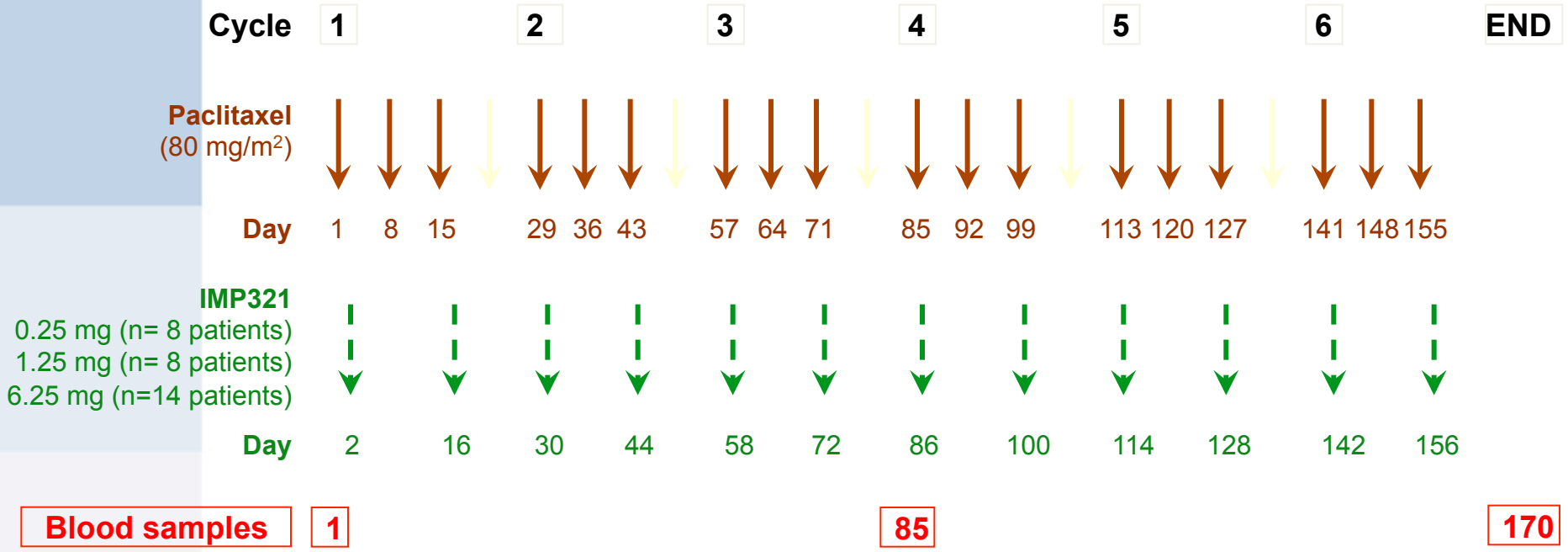
Chemo-immunotherapy in MBC

Administration Schedule

- Weekly paclitaxel, 3 weeks out of 4, combined with IMP321 every two weeks, the day after paclitaxel.
- Blood samples drawn before paclitaxel on Days 1 and 85 and at the final visit - testing the *residual effect* of IMP321 13 days after injection.



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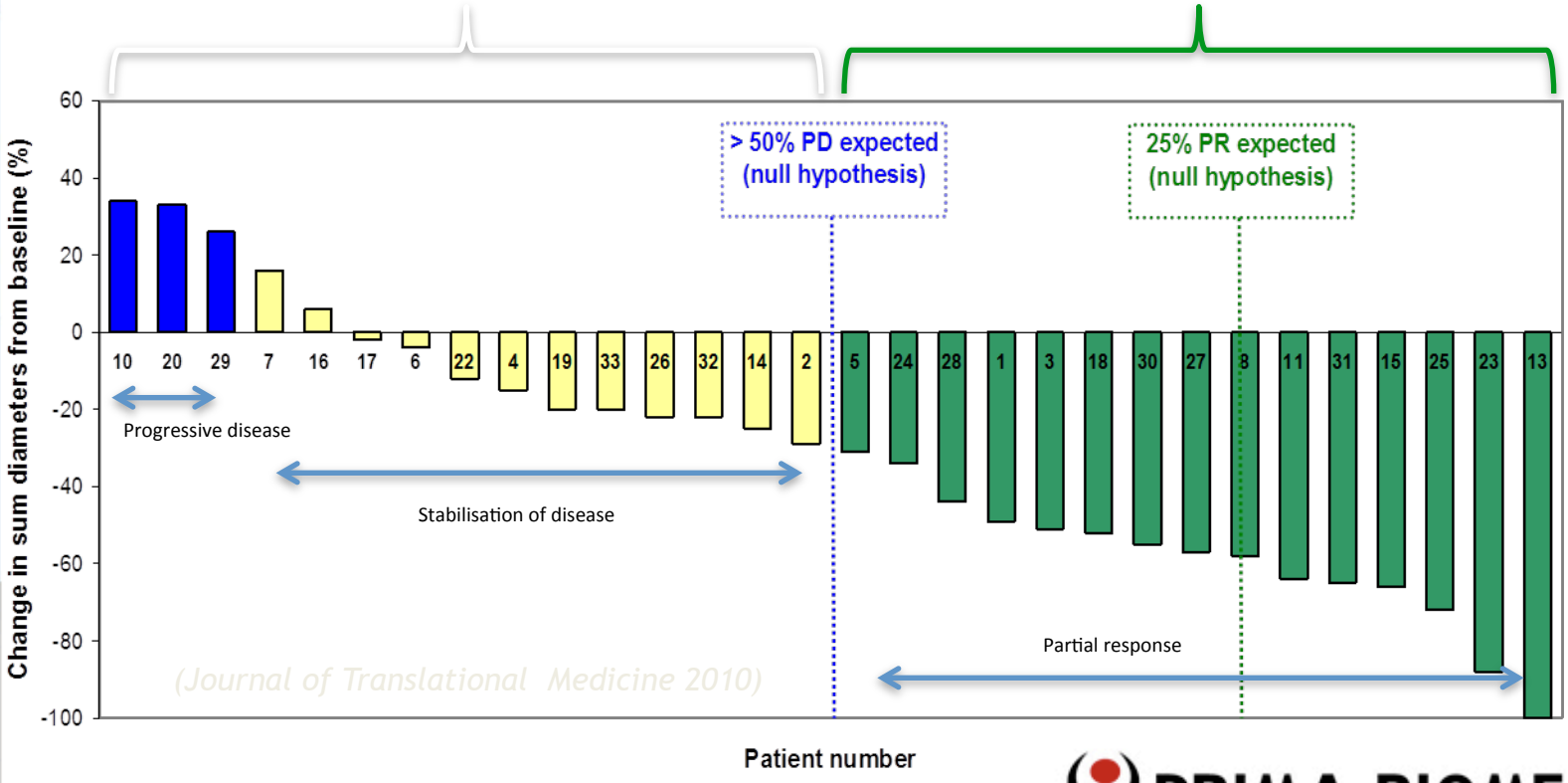
Clinical response rate at six months in mBC

Compared to the historical control group (254 patients with measurable disease at baseline on weekly, 3 weeks out of 4, paclitaxel (ECOG 2100 study)

Clinical benefit: Only 10 % of IMP321 patients progressed in contrast to more than 50% of patients in the historical control group

A 50% response rate was observed in IMP321 patients versus 25% in the historical control group receiving chemotherapy alone



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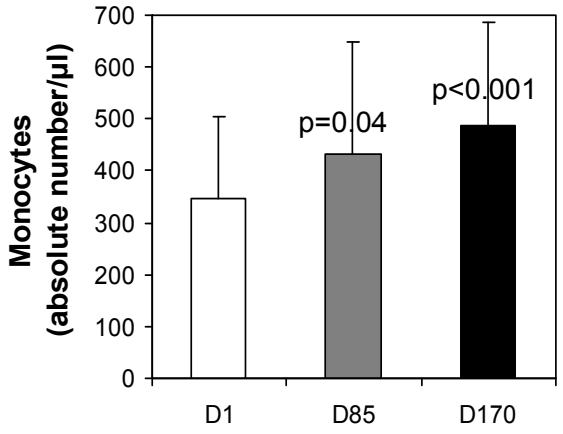
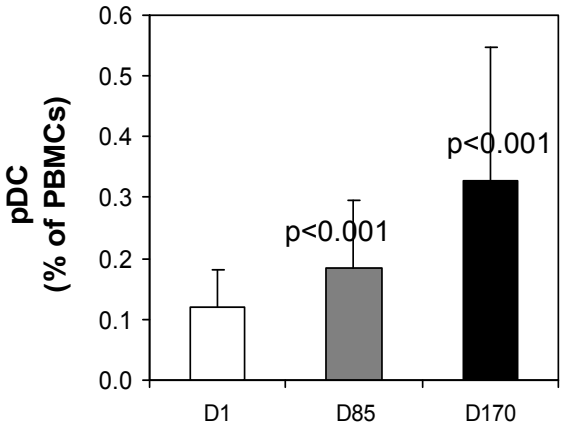
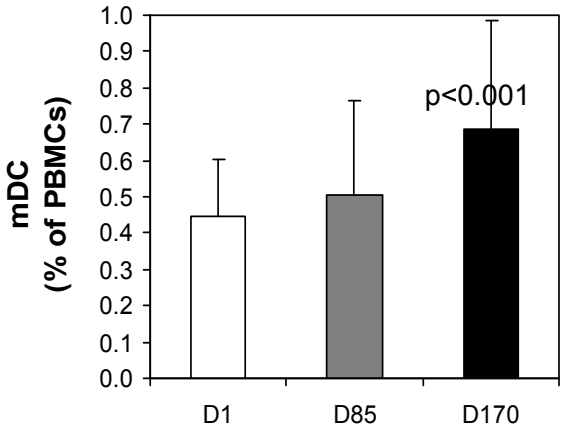
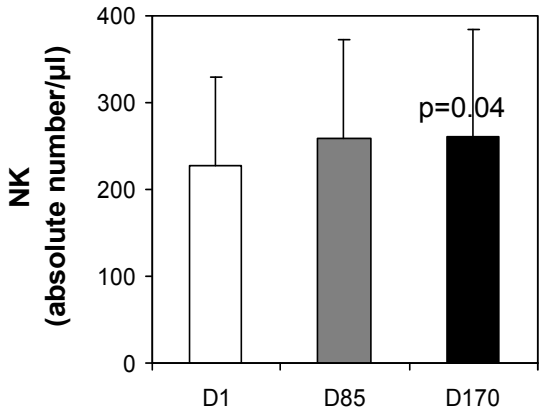
IMP321 induces a sustained increase in primary target cells (MHC class II$^+$ monocytes and DC) and secondary target cells (NK and CD8 T cells)

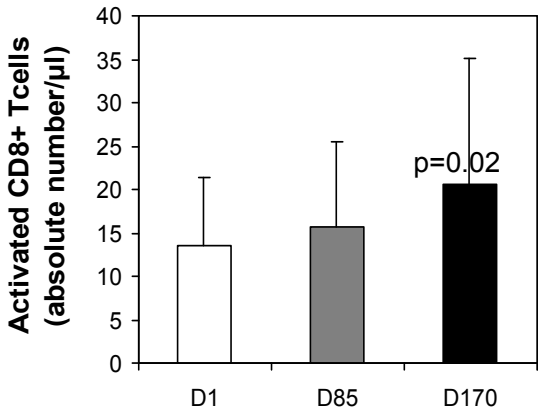
- Increased monocyte, dendritic cell, NK and memory CD8 T cell counts
- Sustained for at least six months as samples are analyzed 13 days after the last injection (i.e. just before the next IMP321 injection)

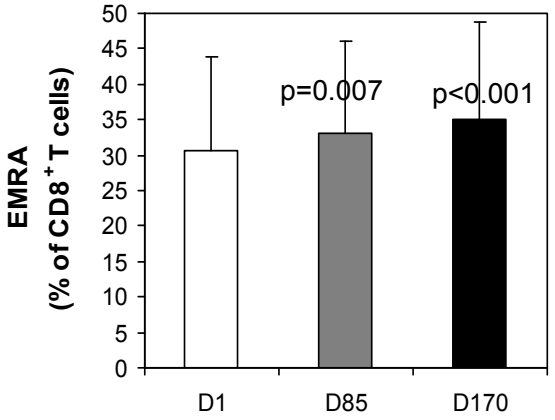






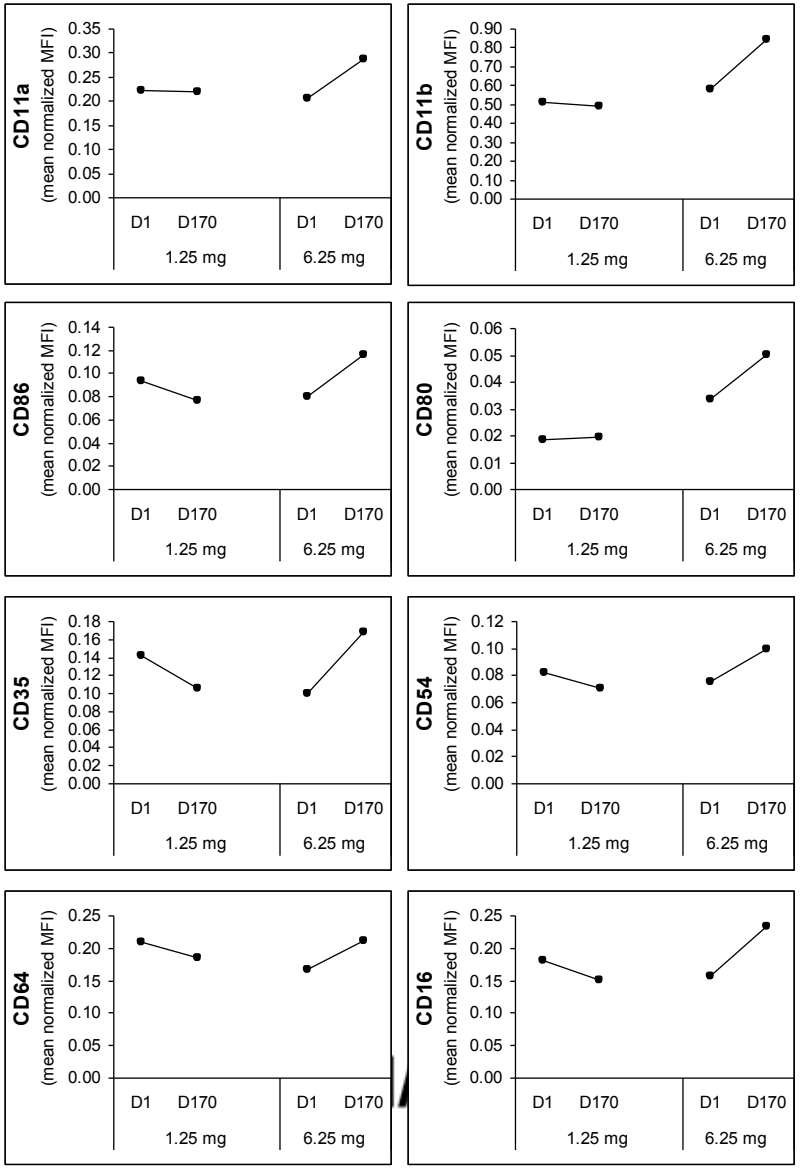






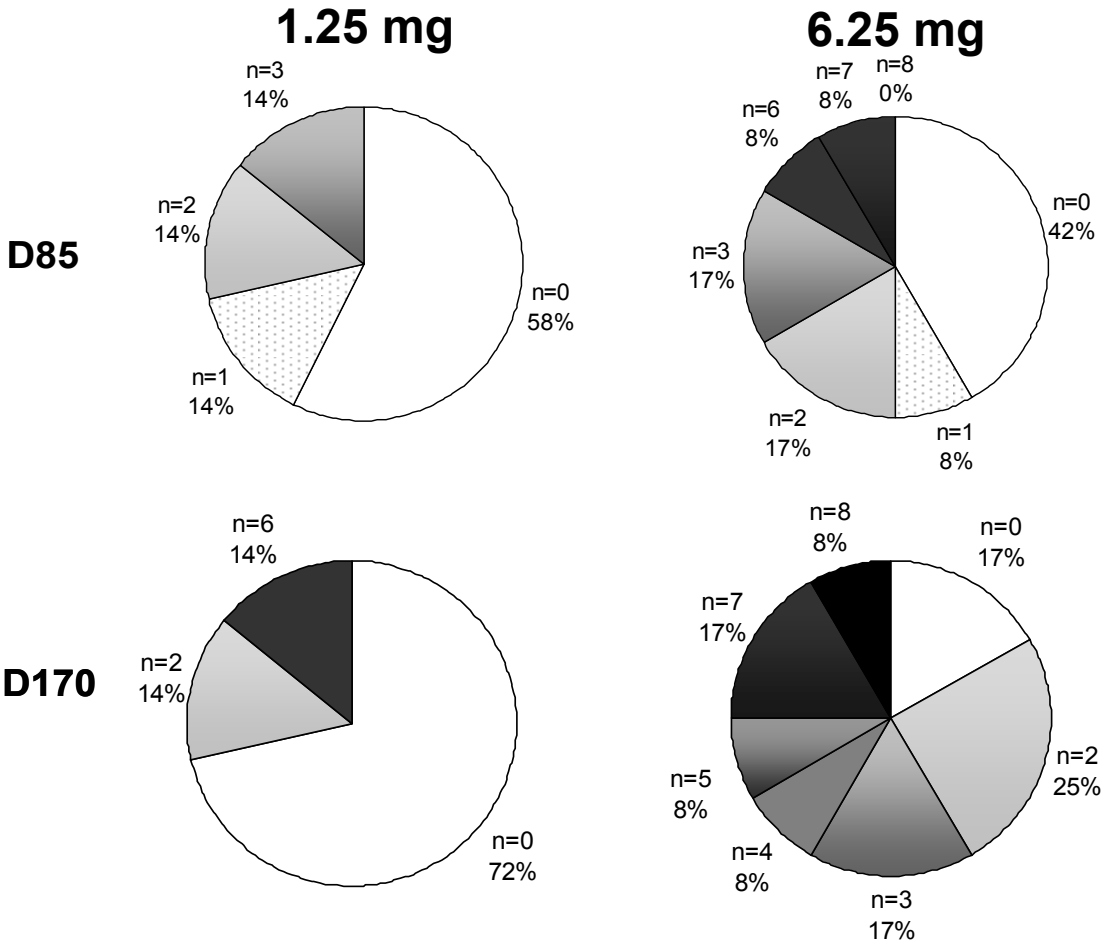
Activation of monocytes by IMP321: all markers are up

- 8 activation markers analyzed on fresh CD14+ whole blood cells: CD11a, CD11b, CD16, CD35, CD54, CD64, CD80 and CD86
- IMP321 dose-response activation of residual monocyte responses at day 13 post-injection in all 8 cases (D170 versus D1)
- Activation sustained for months as samples are analyzed 13 days after the last injection (i.e. just before the next IMP321 injection)



Activation of monocytes by IMP321 is dose-dependent

- Increased gain of function for monocytes: IMP321 dose-response activation
- n = the number of increased (>50 % increase in expression) activation markers out of 8 (CD11a, CD11b, CD16, CD35, CD54, CD64, CD80, CD86)

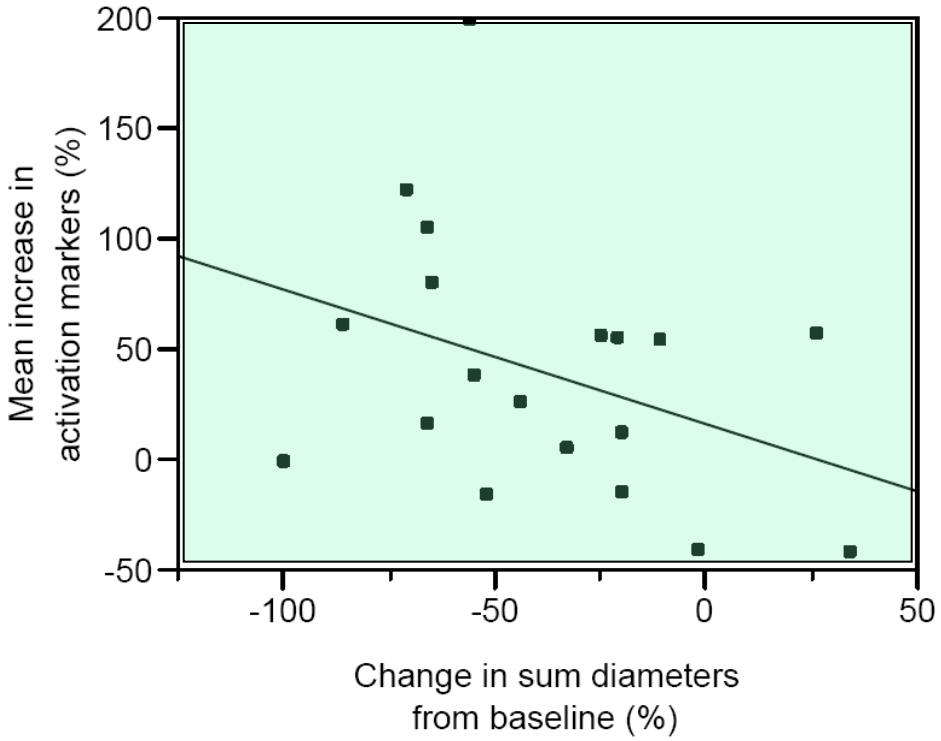


% of patients with increased gain of function

(Journal of Translational Medicine 2010)

Monocyte gain of function is correlated with increased tumor regression

- Significant correlation between gain of function (activation of monocytes) and tumor response.



(Journal of Translational Medicine 2010)

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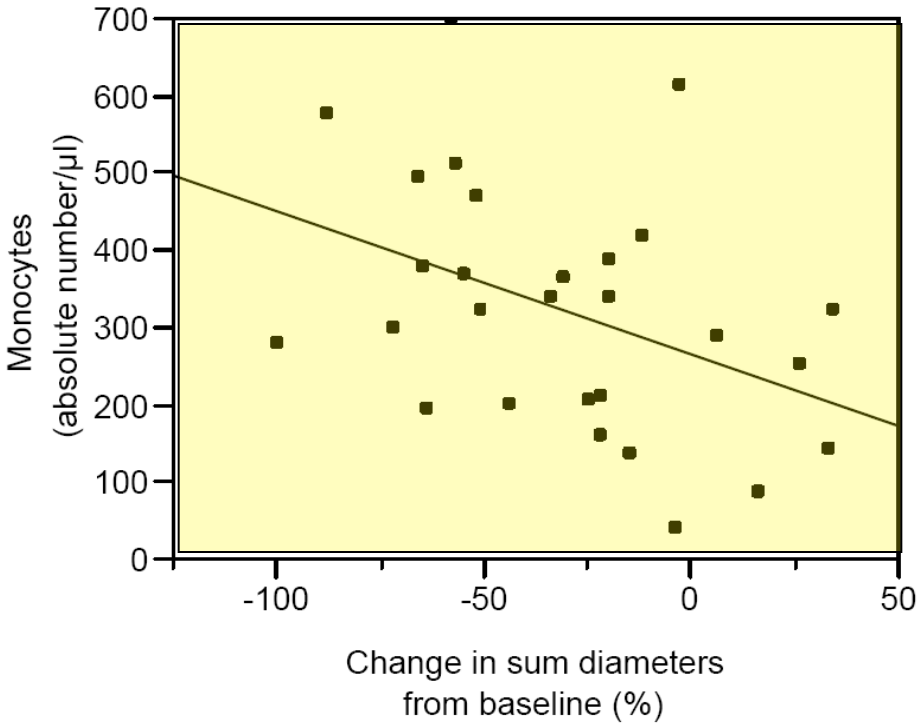
Correlation with Monocyte Counts before Treatment

More evidence of immune involvement

- Clinical response is correlated with monocyte count at day 1



(Journal of Translational Medicine 2010)

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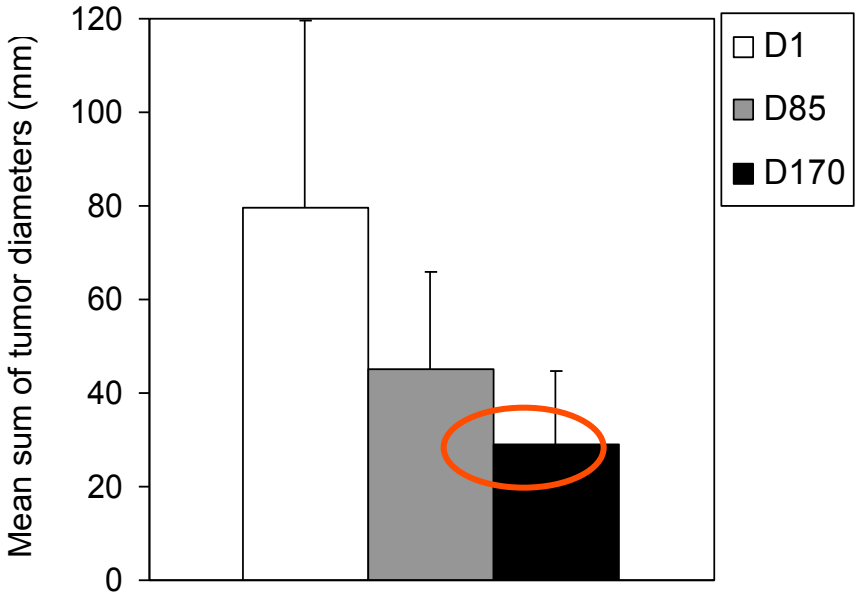
The "Late Response Effect"

More evidence of immune involvement

- Further tumor regression between day 85 and day 170 *which is not seen with chemo alone*
- Such late responses are *characteristic of immunotherapy*



(Journal of Translational Medicine 2010)

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Future plans for IMP321

- Completion of IMP321 manufacturing in 1st half 2015
- Start of **new clinical trials with IMP321:**
  - **Phase IIb AIPAC trial** in metastatic breast cancer (double blind, placebo-controlled study)
  - **Phase I TACTI-mel trial** in combination with a PD1 inhibitor in melanoma

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AIPAC – Overall Study Design

Title

AIPAC (Active Immunotherapy PAClitaxel): A multicentre, Phase IIb, randomised, double blind, placebo-controlled study in hormone receptor-positive metastatic breast carcinoma patients receiving IMP321 (LAG-3Ig fusion protein) or placebo as adjunctive to a standard chemotherapy treatment regimen of paclitaxel.

Design

- Open label, dose escalation (run-in stage)
- Randomized, double-blind, placebo-controlled (Phase IIb stage)
- 211 breast cancer patients (stage IV, hormone receptor-positive)
- Paclitaxel + IMP321 vs. paclitaxel + placebo

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THANK YOU

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