

An active immunotherapy combined with first-line weekly paclitaxel in metastatic breast cancer: first results of IMP321 (LAG-3Ig) as an antigen presenting cell activator in the AIPAC phase IIb trial



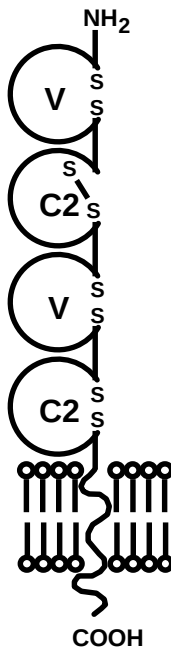
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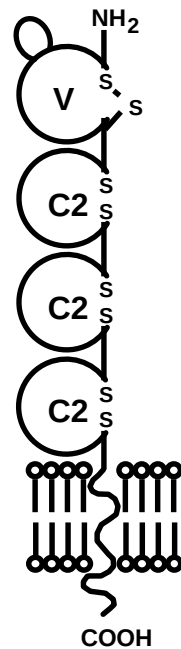
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Lymphocyte Activation Gene-3 (LAG-3 or CD223)

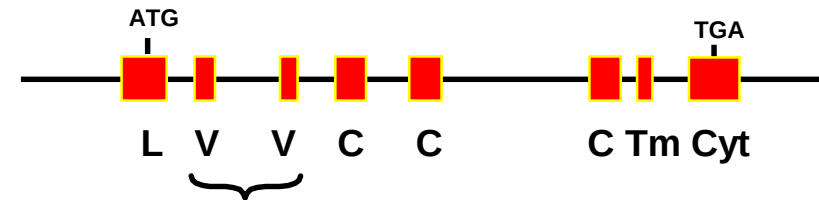
CD4



LAG-3

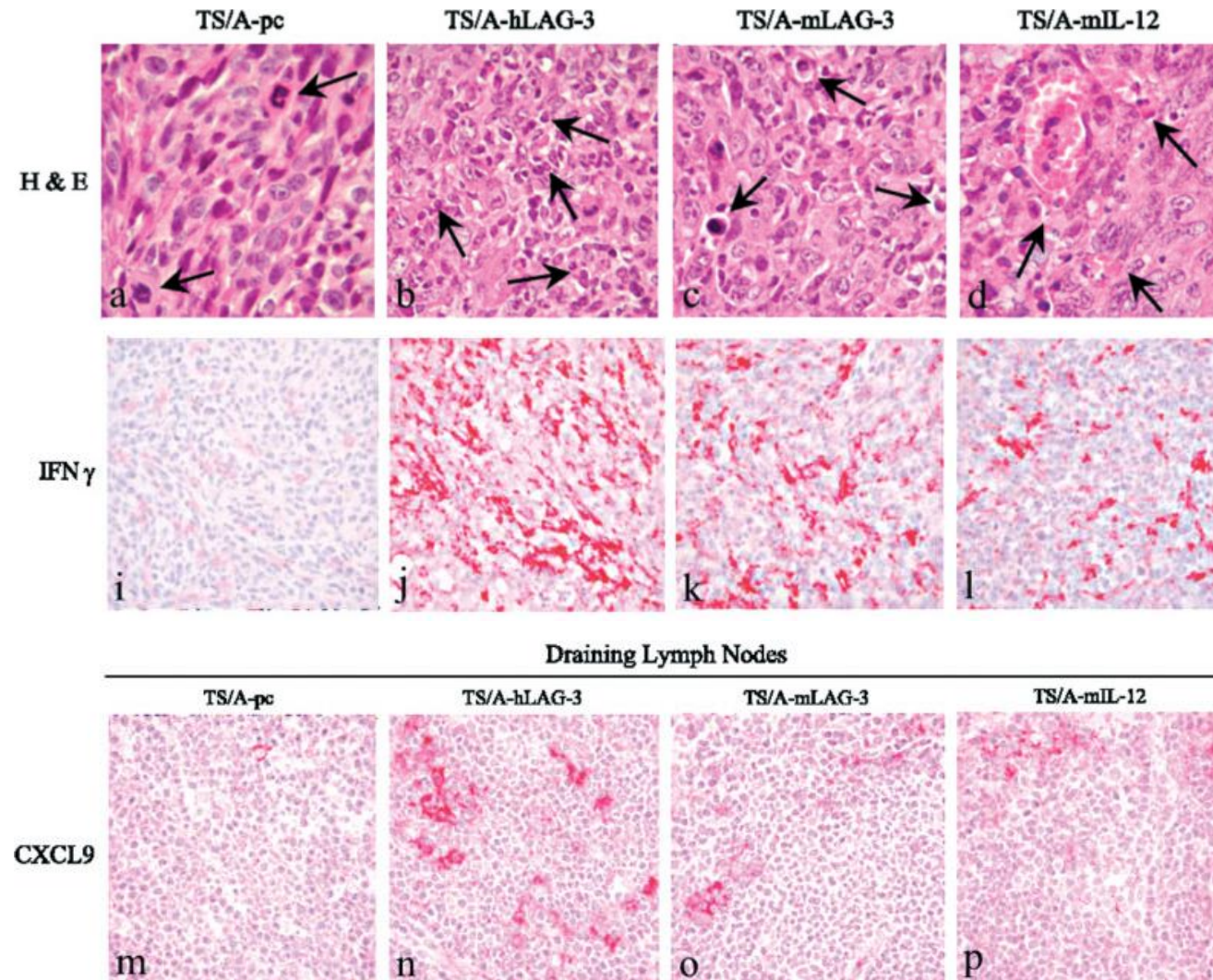


Genomic LAG-3 1 kb

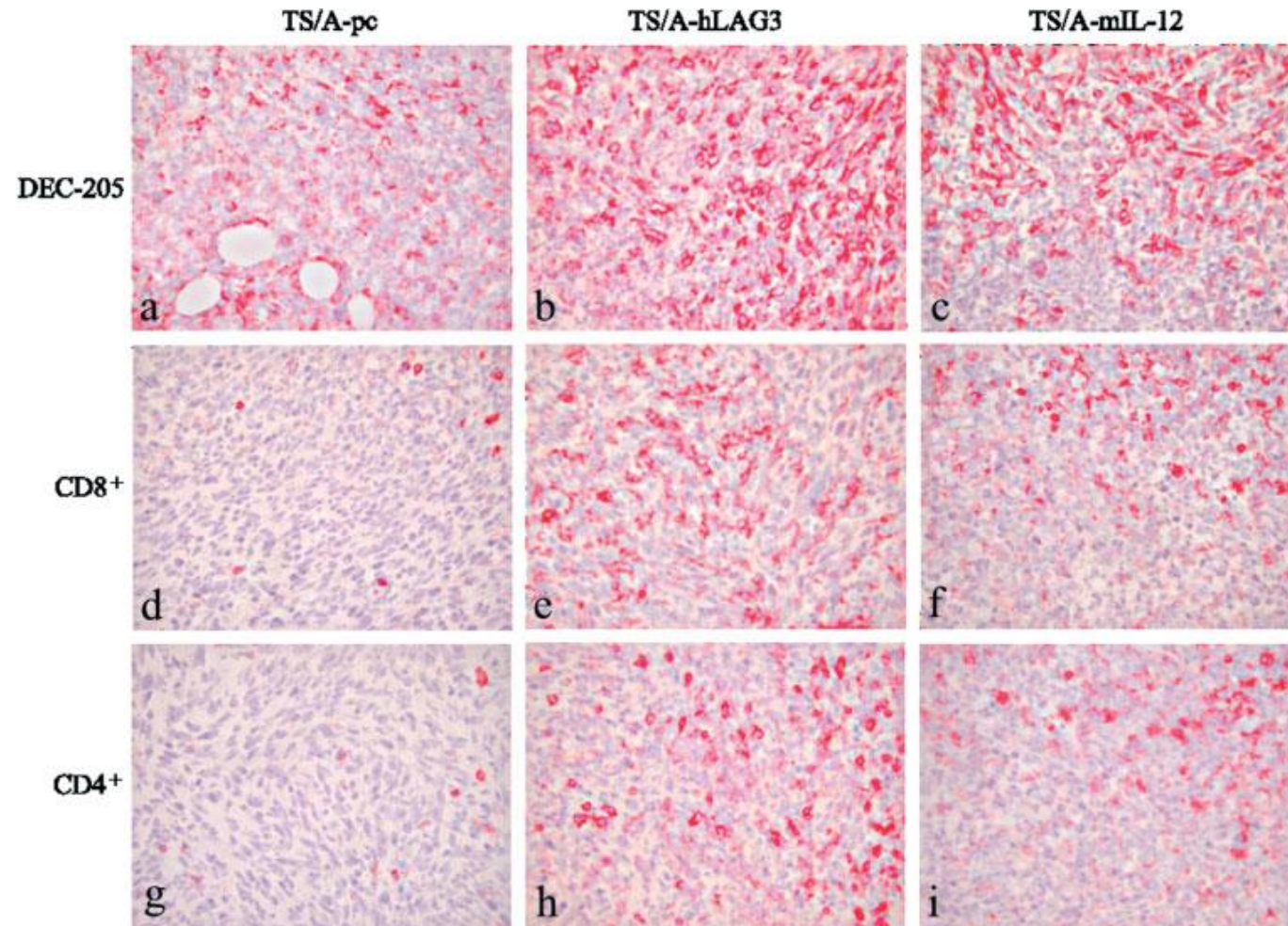


- 4-IgSF domain transmembrane proteins.
- Same genomic organization (intron in D1, duplication event D1D2 vs D3D4)
- Close proximity on 12p13.

Immunological mechanisms elicited at the tumour site
by LAG-3 versus IL-12:
sharing a common Th1 anti-tumour immune pathway

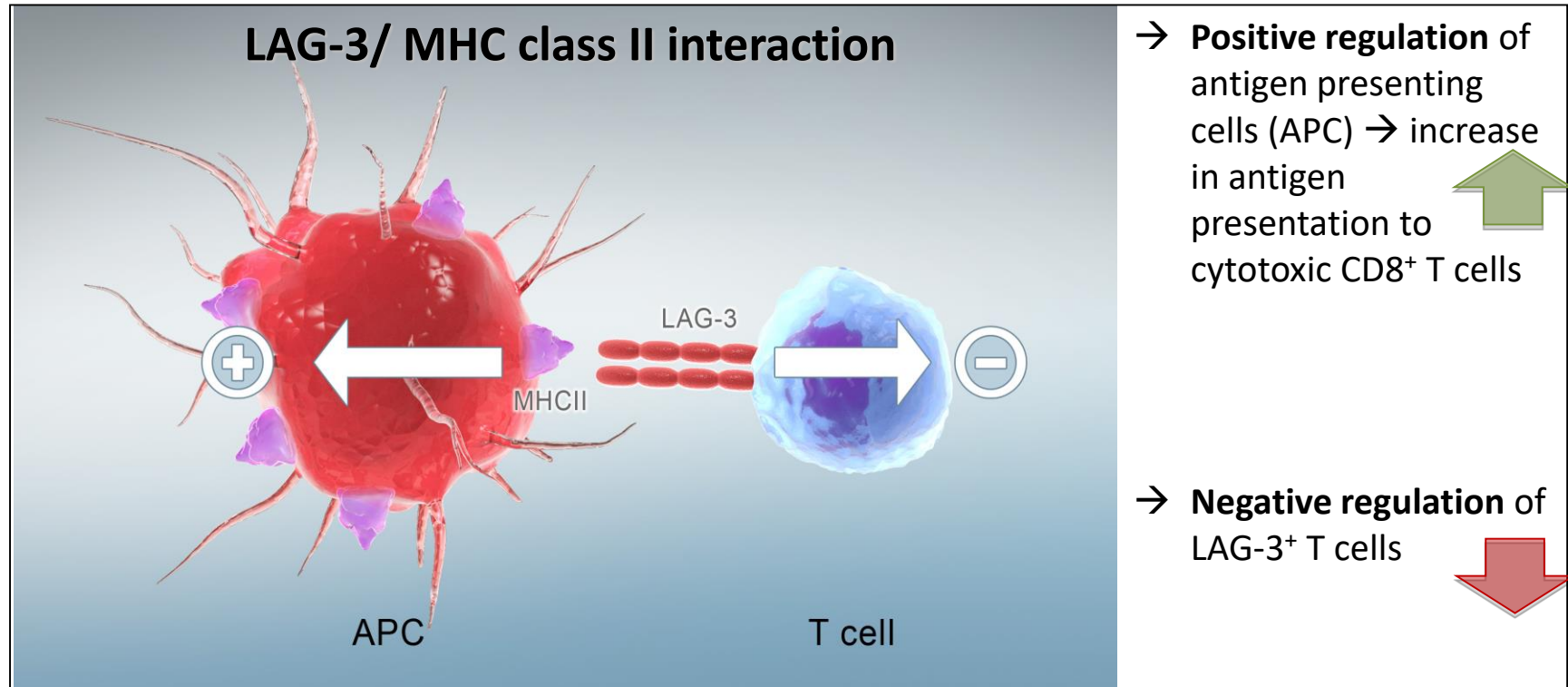


Immunological mechanisms elicited at the tumour site
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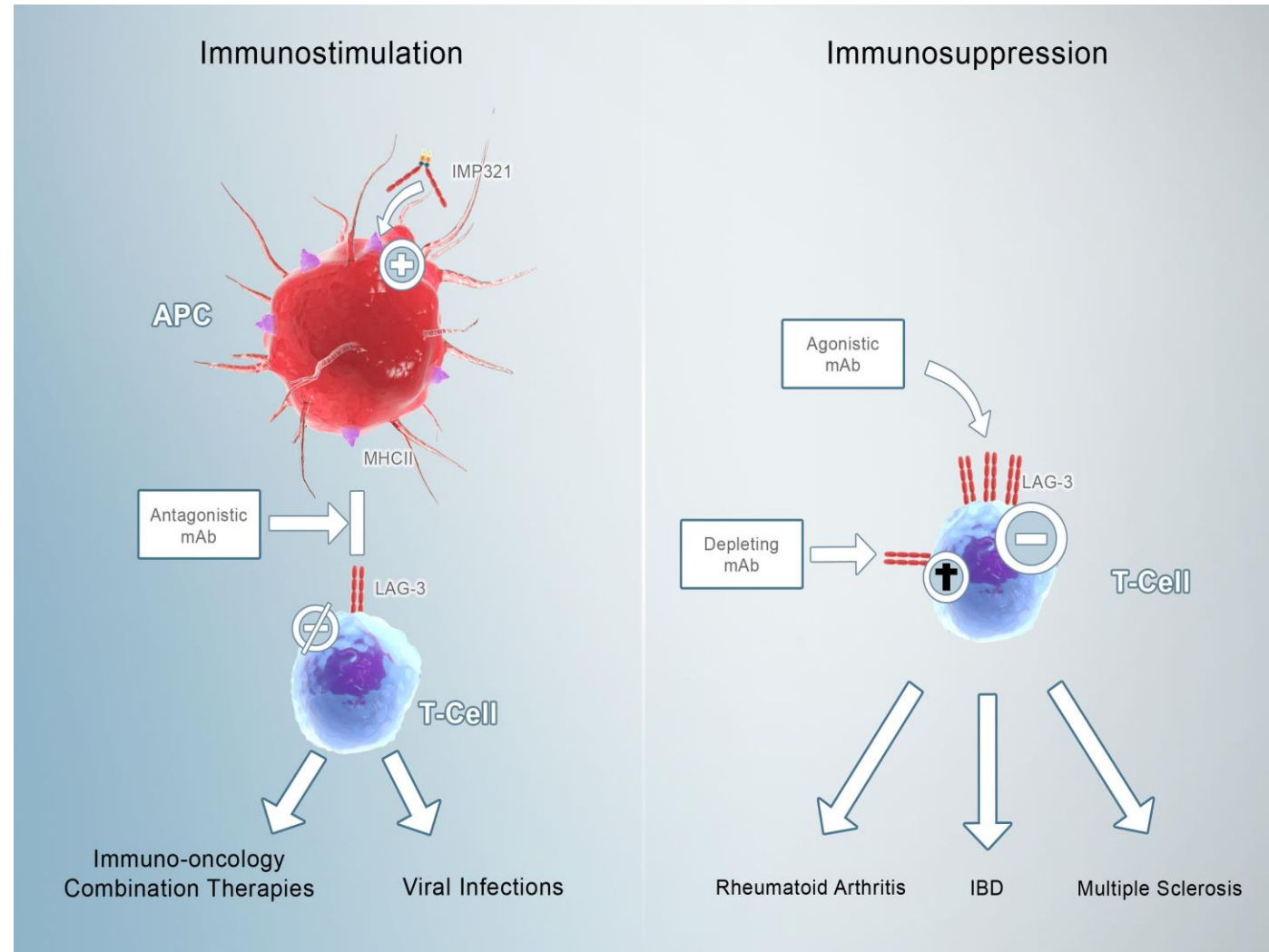


LAG-3 As a Therapeutic Target

- LAG-3 is widely expressed on tumor infiltrating lymphocytes (TILs) and cytotoxic T cells
→ Prime target for an immune checkpoint blocker (such as PD-1)
- Functionally similar to CTLA-4 (targeted by Yervoy®) and PD-1 (Keytruda®)

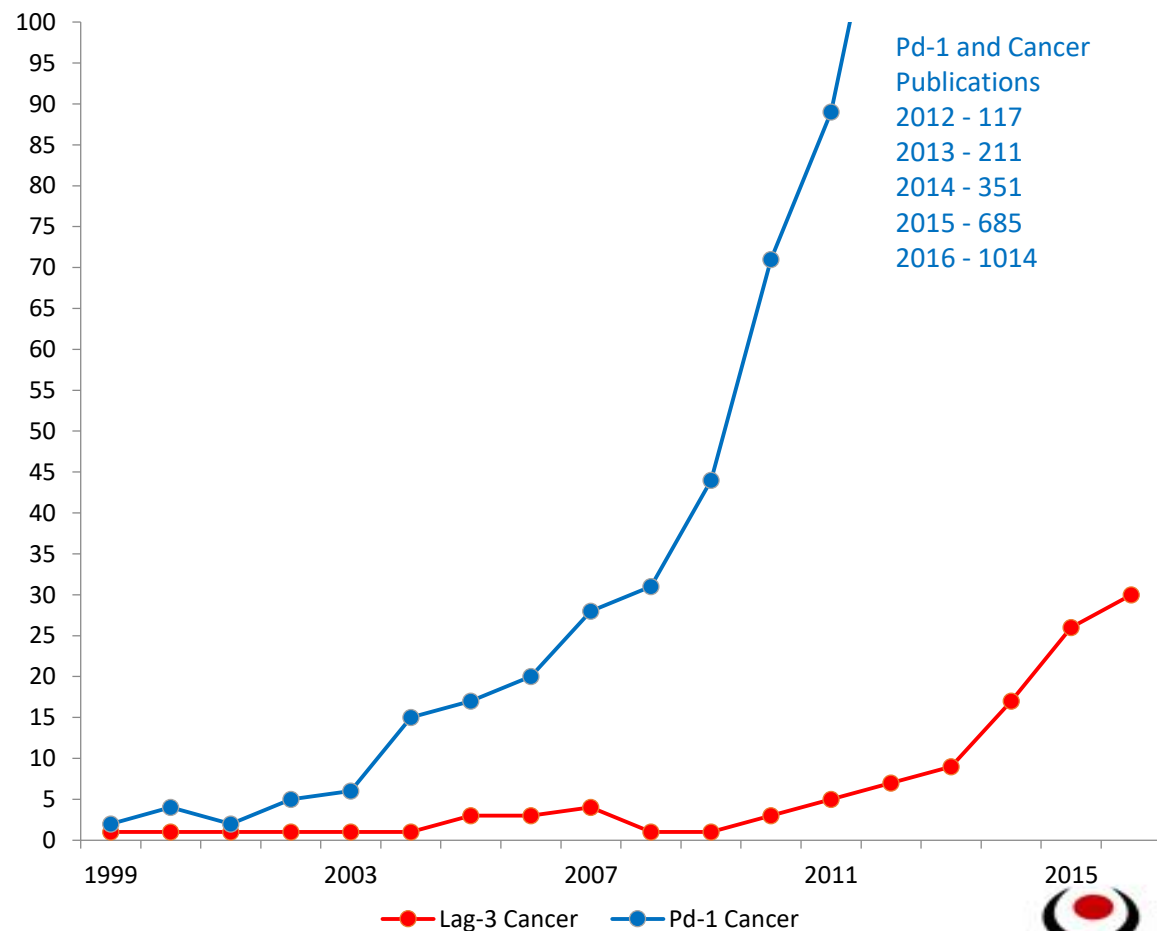


Targeting LAG-3 May Lead to Multiple Therapeutics in Numerous Indications



Growing Interest in LAG-3

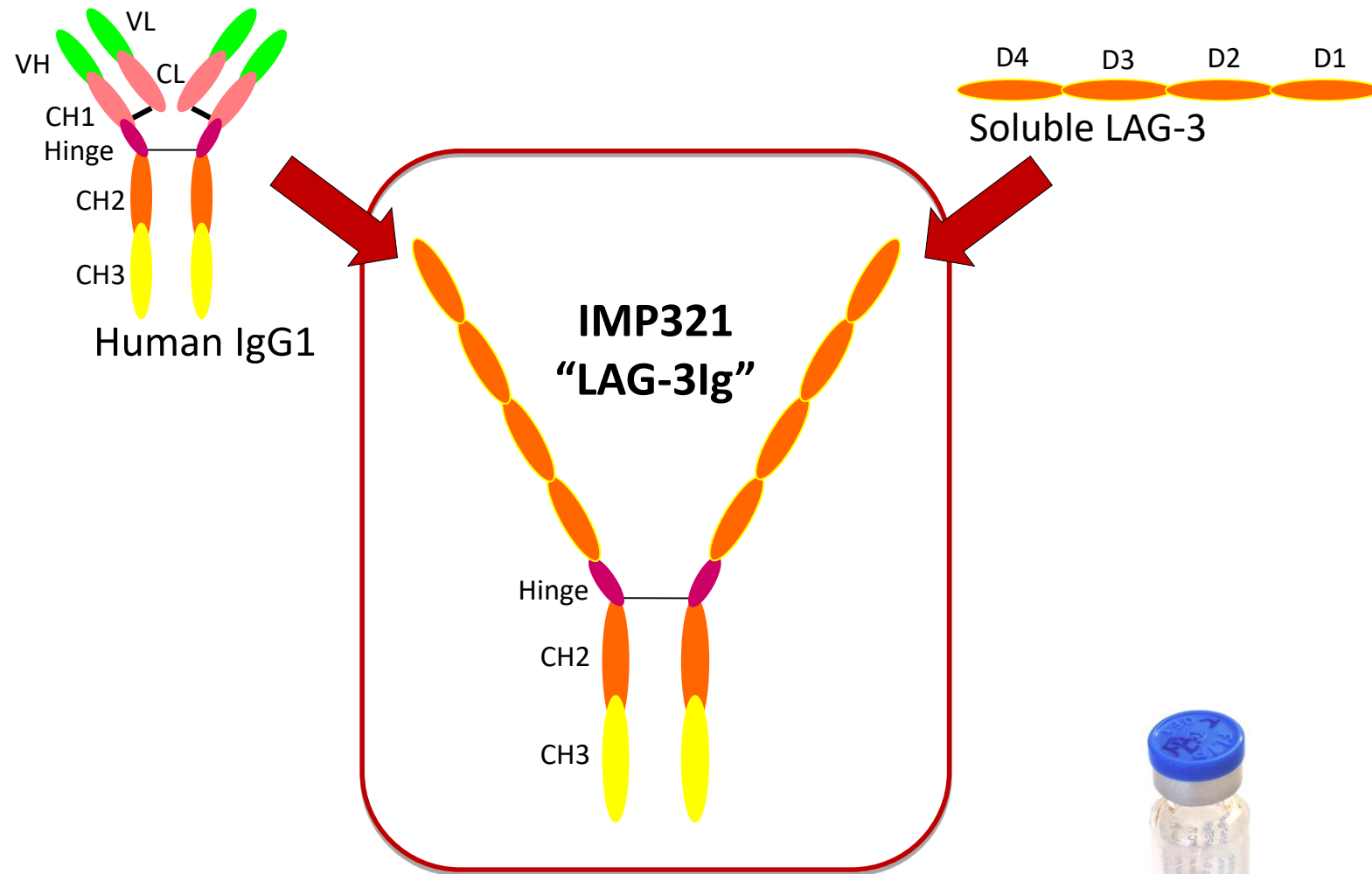
- Overall understanding and appreciation of the importance of LAG-3's role in the immune system continues to grow
- Trajectory of the PubMed articles on „LAG-3 cancer“ is similar to that of „PD-1 cancer“



LEAD PRODUCT IMP321



IMP321

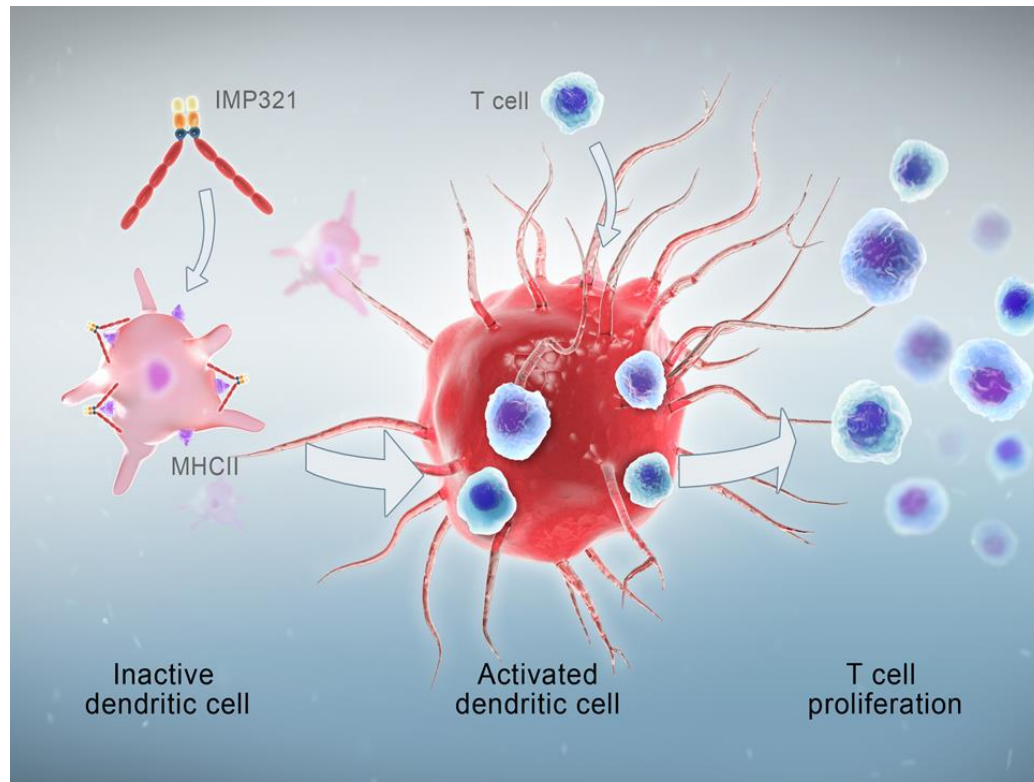


- **Soluble recombinant form of LAG-3**
- Human fusion protein
- Dimeric, very stable, high affinity for DC
- Antigen presenting cell (APC) activator
- **Unique and first-in-class**



IMP321

Soluble dimeric recombinant form of LAG-3Ig (fusion protein)



→ IMP321 binds to MHC class II on monocytes

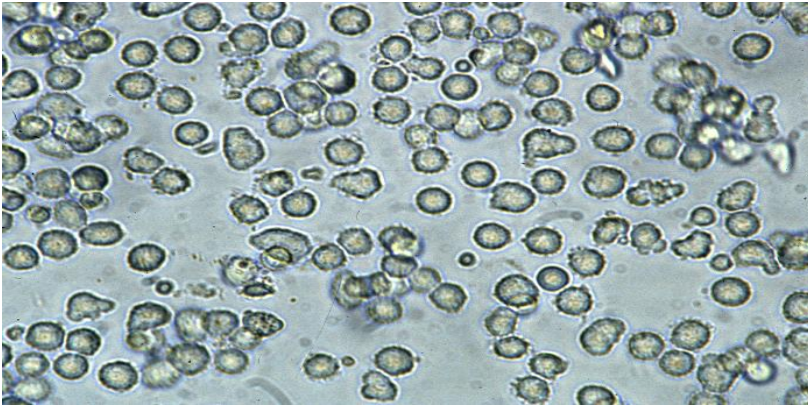
→ DC/monocyte activation induced

→ Leads to T cell expansion and proliferation

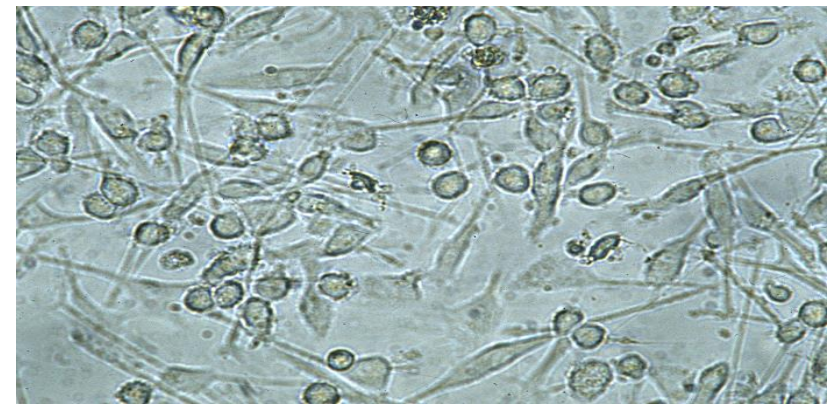
- Highly efficacious in multiple animal models of cancer and infectious disease
- Shown to be safe, non-immunogenic and efficacious in humans

IMP321 as an MHC class II agonist

mDC + hIgG1 (negative control), 4 hrs



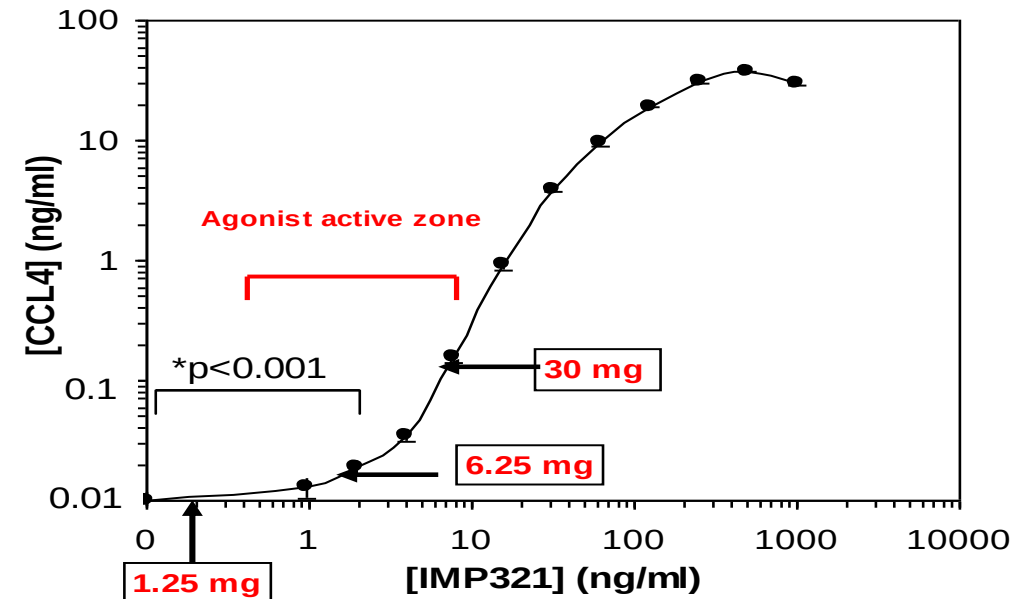
mDC + 1 µg/ml LAG-3Ig, 4 hrs



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

IMP321 as an MHC class II agonist

In vitro bioactivity of IMP321. IMP321 potency to induce CCL4 (MIP-1 β) 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 $\pm$ 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.



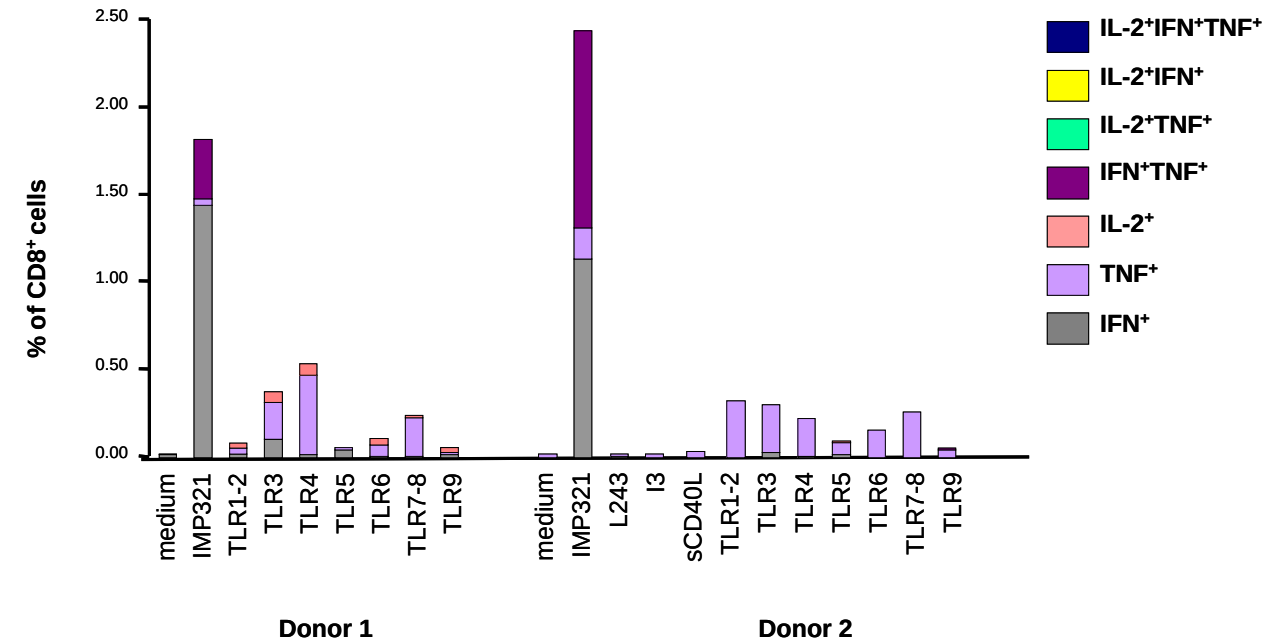
IMP321 induces a better Tc1 differentiation than sCD40L or TLR agonists

➤ Human blood lymphocytes are analyzed in a 16 hr *ex vivo* assay

➤ Intracellular staining of CD8 T cells

➤ Only IMP321 induces IFN⁺ CD8 T cell responses

➤ TLR agonists but not IMP321 induce IL-10 production which suppresses Tc1 differentiation



IMP321 – Potential Applications

Potential combination therapy strategies:

- **Chemo-immunotherapy** in various cancer indications
 - Combination therapy with active agents such as Taxanes (e.g. Paclitaxel), anthracyclines, alkylating agents, anti-metabolites, vincas...
- **I-O combination** in various cancer indications
 - With PD-1, PDL-1 or CTLA-4 antagonists...
- **Cancer vaccine**
 - To locally stimulate the immune system

IMP321 Clinical Trials Overview

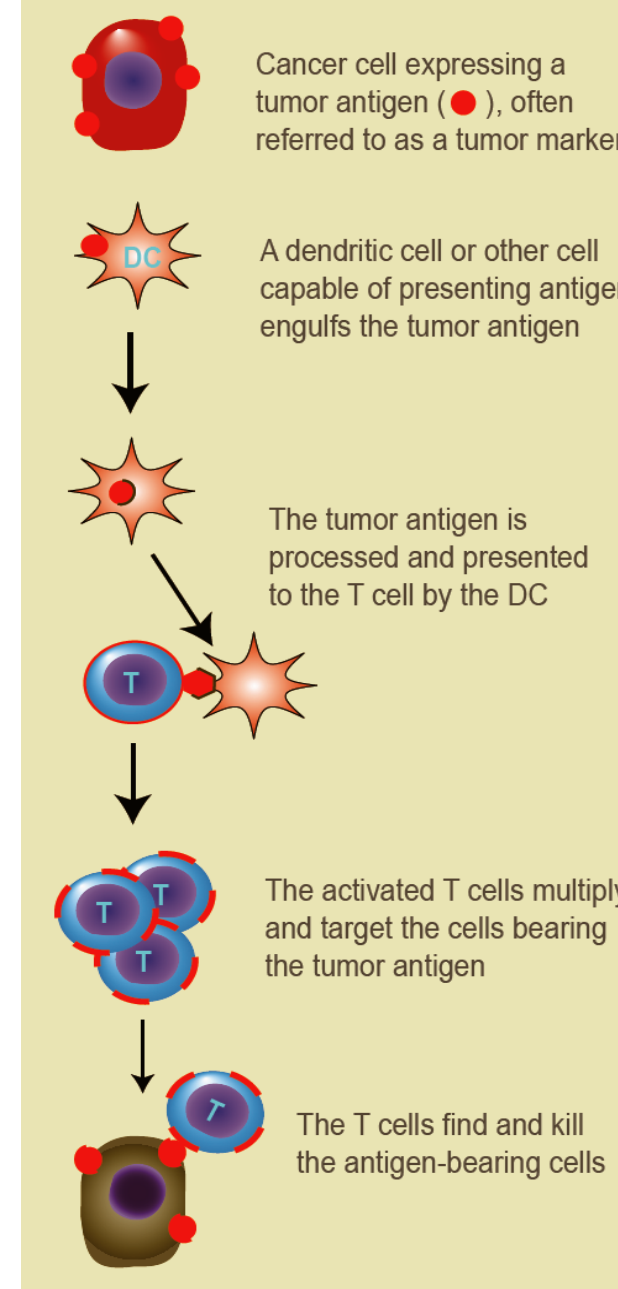
Protocol	Patient Population	Compound	Status
P001 Phase I	healthy males	IMP321 (adjuvant)	Completed
P002 Phase I	healthy males	IMP321 (adjuvant)	Completed
P003 Phase I	metastatic renal cell carcinoma	IMP321 (monotherapy)	Completed
P005 Phase I	metastatic breast carcinoma	IMP321 (chemo-immunotherapy)	Completed
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

Introduction to chemo-immunotherapy

Part I: chemotherapy alone induces an immune response against the tumour

Chemotherapy induces an immune response

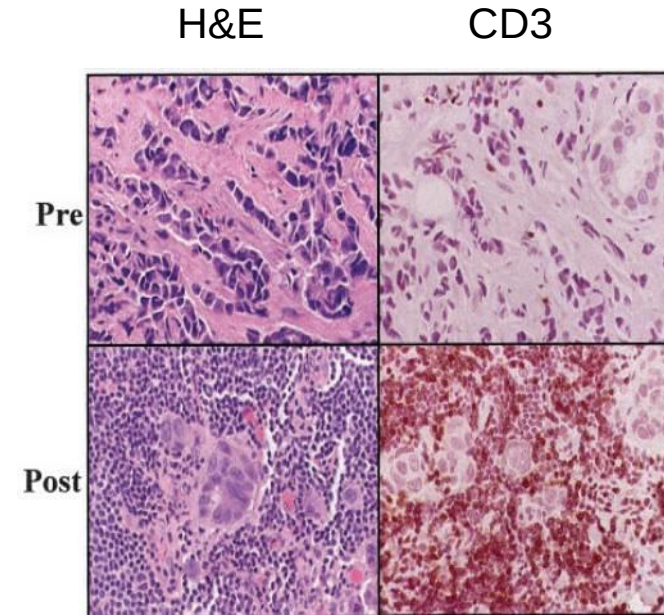
- Chemotherapy alone induces effective anti-cancer T cell responses through the release of large amounts of antigenic tumour cell debris
- Chemo + active immunotherapy (APC activators, cytokines, cancer vaccines): an emerging market based on a different MoA (T-cell killing of tumour cells)
- Therefore, boosting the function of antigen-loaded APC by APC activators is synergistic to the action of chemotherapy



The immunoadjuvant effect of chemotherapy

Massive tumour infiltration by T cells after chemotherapy alone

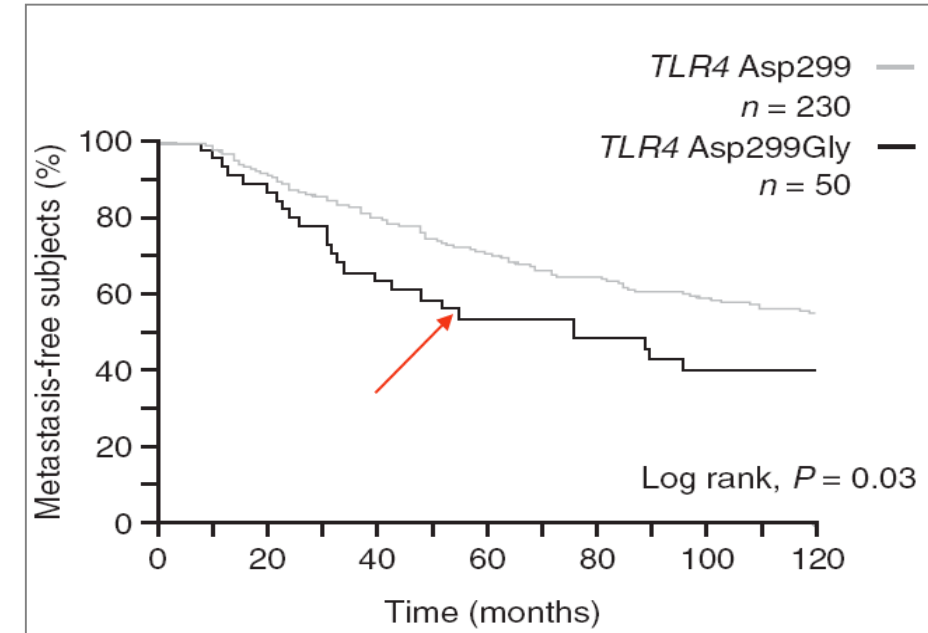
- Neoadjuvant paclitaxel in locally advanced breast cancer before surgery
- At 2-3 weeks (surgery), induction of Tumour Infiltrating Lymphocytes (“TILs”) in
 - 67 % of the CR,
 - 25 % of the PR
 - 0 % of the SD patients



(Clin.Cancer Res. 2001, 7:3025)

A defect on APC function induces a lower response to chemotherapy

TLR4 dictates the efficacy of anti-tumor chemotherapy in humans. Kaplan-Meier estimates of time to metastasis between two groups of patients bearing the normal or mutated TLR4 alleles. The time to progression was analyzed in 280 women with nonmetastatic breast cancer with lymph node involvement who were treated by surgery followed by anthracycline-based chemotherapy and local irradiation.



In breast cancer patients who receive adjuvant chemotherapy, the analysis of metastasis-free survival showed an overall significantly lower percentage of metastasis-free patients in the group with *mutated* TLR4. The effect of the TLR4 mutation is to reduce antigen-presenting cell function. Such patients could not benefit fully from the immunological component of chemotherapy, i.e. the induction of cytotoxic CD8 T cell responses to tumor antigens released by the dying tumor cells (*Nat. Med.* 2007, 13:1050).

Introduction to chemo-immunotherapy

Part 2: an immunostimulant given after chemotherapy
boosts the immune response against the tumour

Characteristics of chemo-immunotherapy

- APC activators -



Chemo:

- standard therapy for advanced cancer
- objective: maximal killing of tumor cells
- therefore: high dose (toxic effects)
- tumor shrinkage is rapid (<3 months)
- but clinical benefit is short
- induces apoptotic tumor cell death and the release of tumor antigens with suboptimal T cell responses

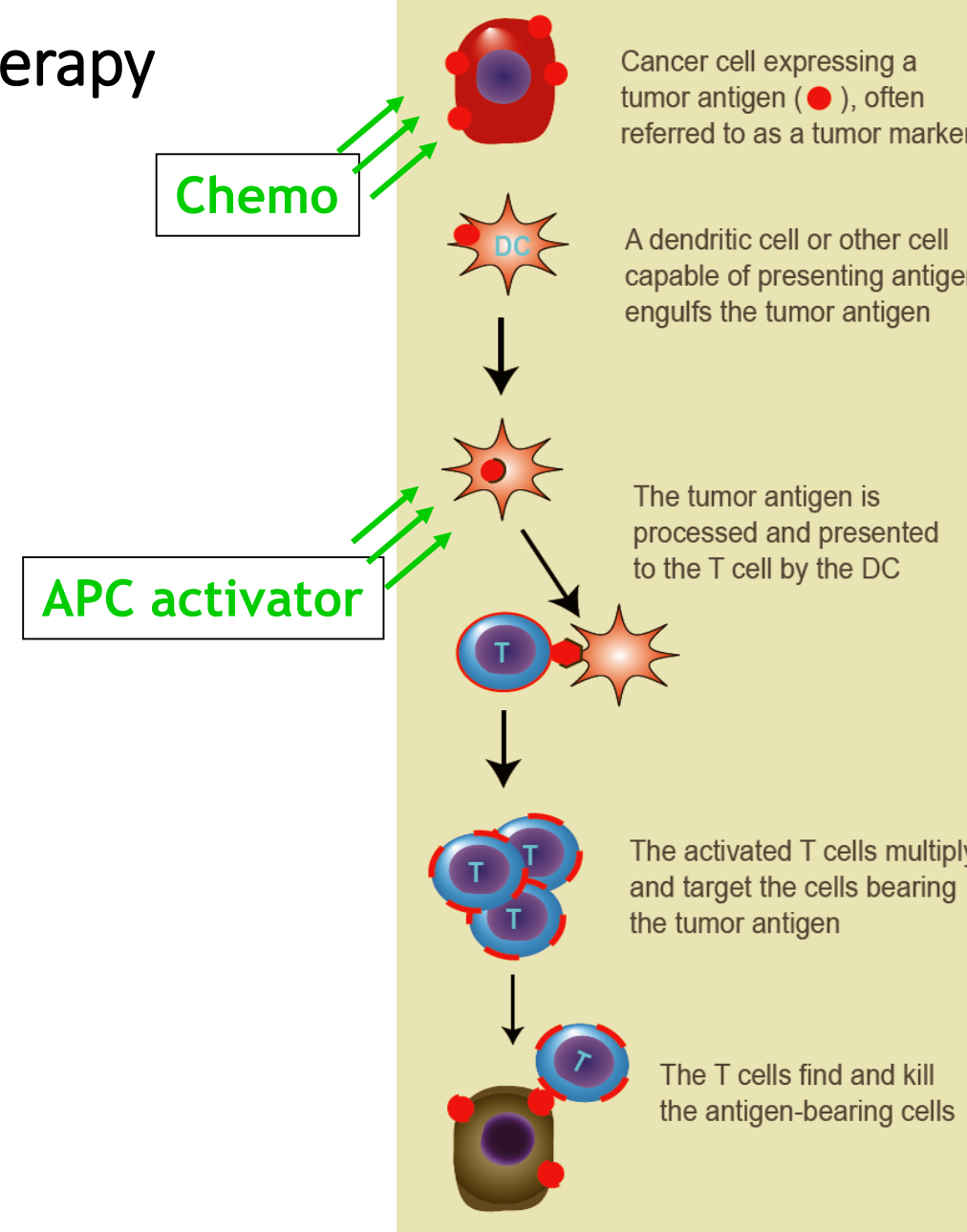


APC activators:

- experimental therapy which should be given with standard therapy in first-line patients
- objective: to build-up progressively T cell responses over time while avoiding auto-immune reactions
- therefore: low dose (no toxic effects)
- tumor shrinkage is slow (>3 months)
- but clinical benefit is durable



Chemo-immunotherapy: a synergistic combination and a new hope for advanced cancer patients



IMP321 in MBC



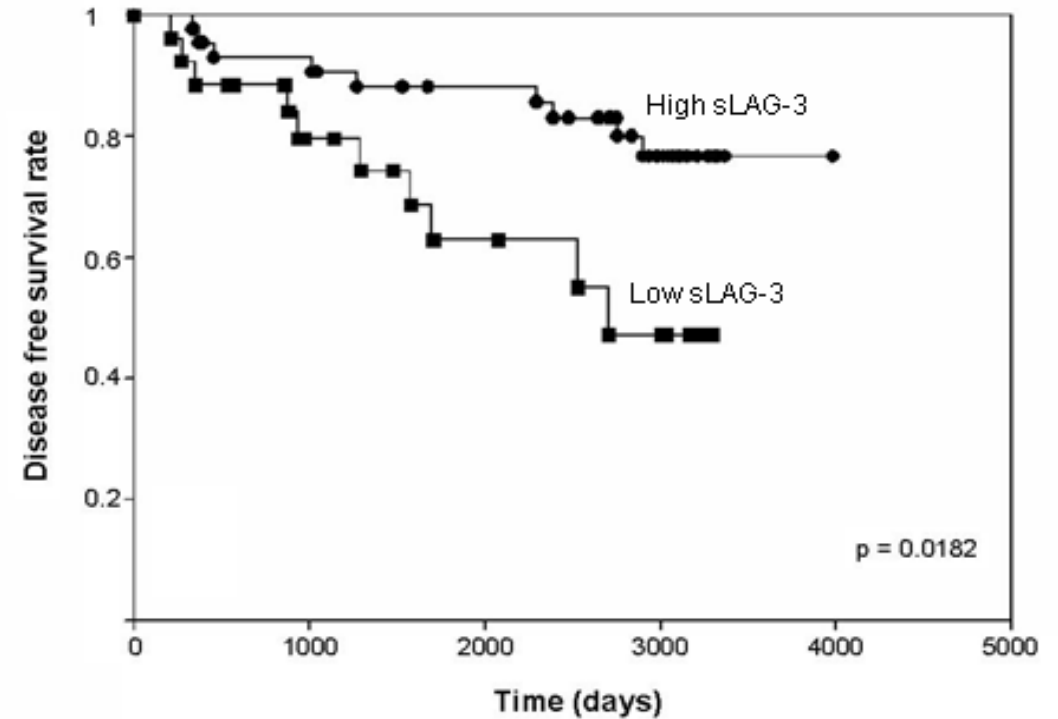
Pre-treatment serum sLAG-3 concentration predicts survival in breast cancer

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.

(*Cancer Lett.* 2006, 235:147)



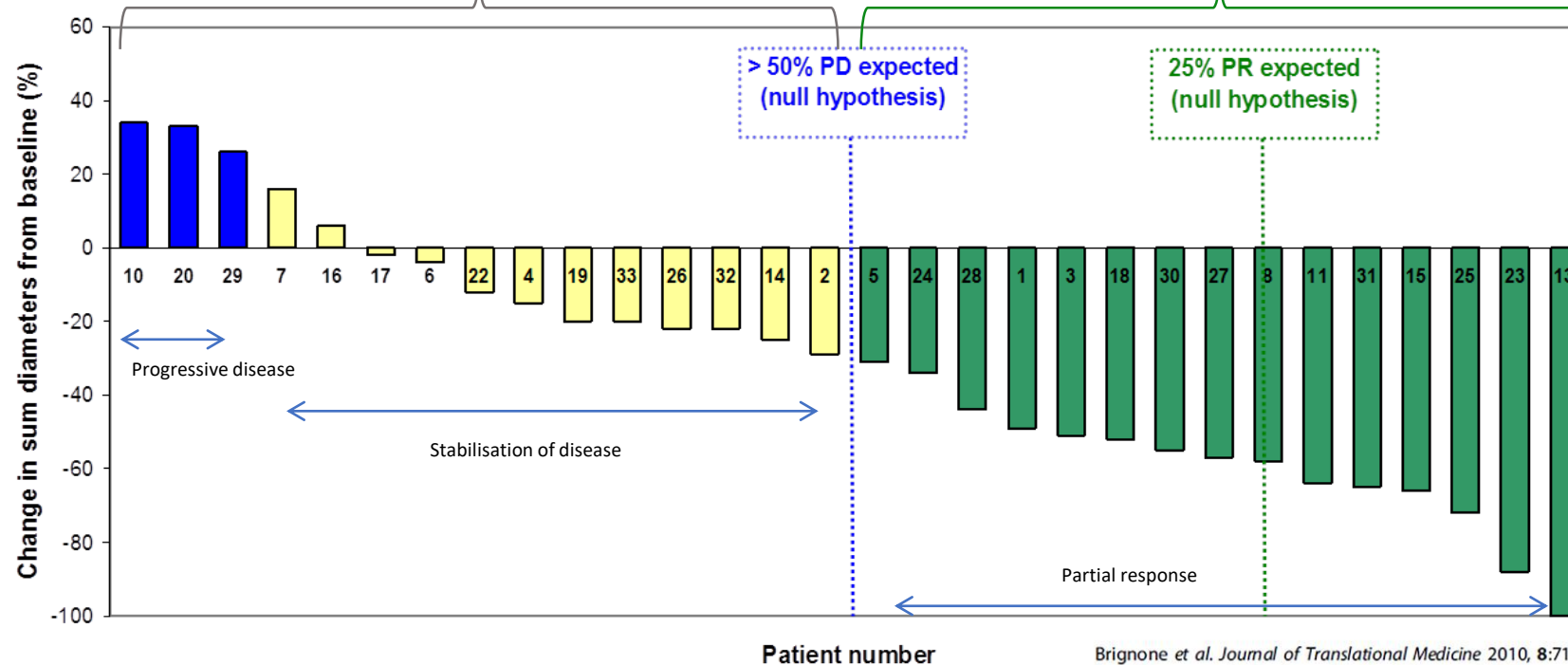
IMP321 in MBC

Completed Studies - Efficacy

Efficacy results of a phase I trial of IMP321 + paclitaxel in MBC compared to historical paclitaxel monotherapy*

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



* 254 patients with measurable disease at baseline on weekly, 3 weeks out of 4, paclitaxel (ECOG 2100 study); J Clin Oncol. 2009 Oct 20;27(30):4966-72.

Brignone et al. Journal of Translational Medicine 2010, 8:71
<http://www.translational-medicine.com/content/8/1/71>

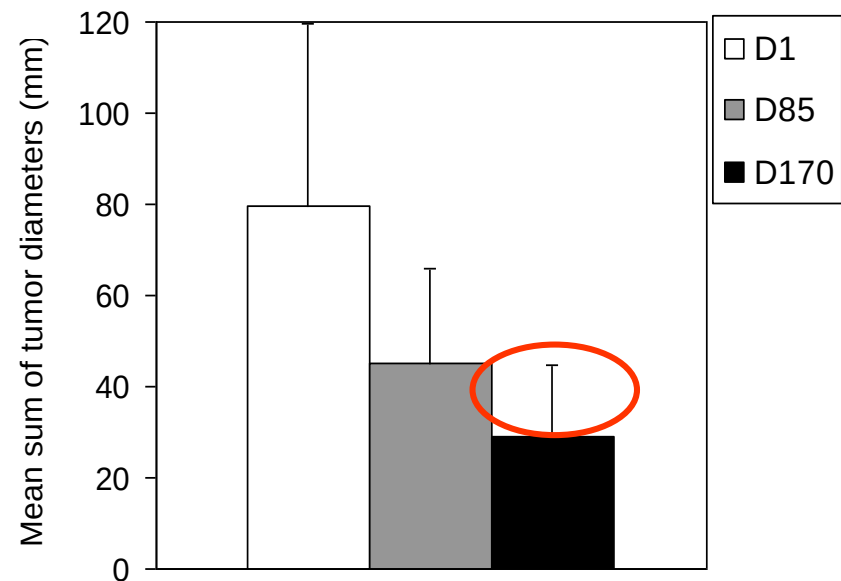
IMP321 in MBC

Completed studies - Efficacy

Efficacy results of a phase I trial of IMP321 + paclitaxel in MBC “Late response effect”

→ Clear evidence of immune involvement

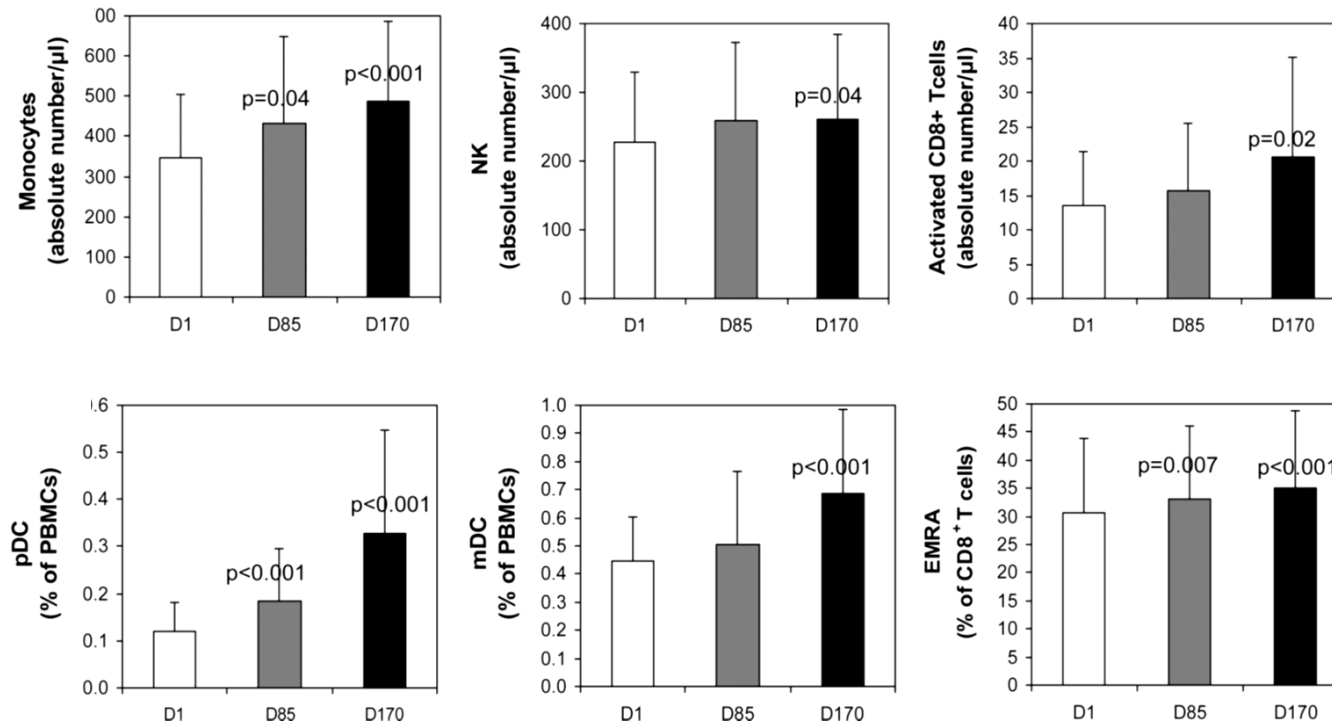
- Further tumor regression between day 85 and day 170 which is not seen with chemo alone
- Such late responses are characteristic of immunotherapy



IMP321 in MBC

Completed studies –“Proof of principle”

- Increased primary (monocytes and dendritic cells (DC)) and secondary target (Natural killer (NK) cells and activated CD8 and memory CD8 T cells) cell counts
- Sustained for ≥ 6 months** (analyzed 13 days after the last injection and before the next IMP321 injection)

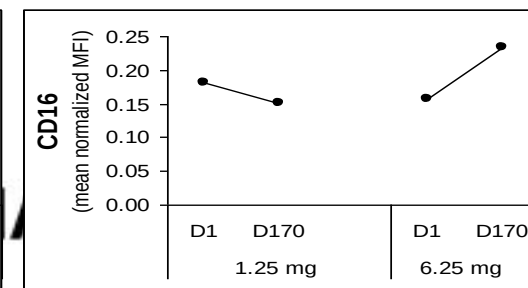
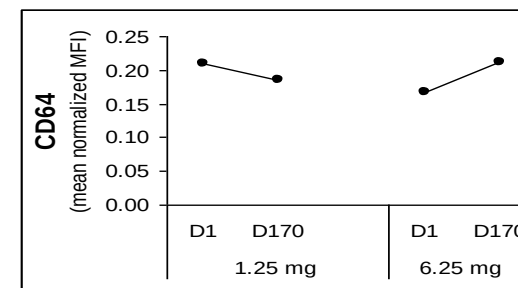
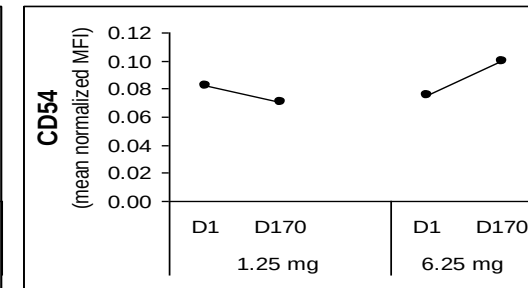
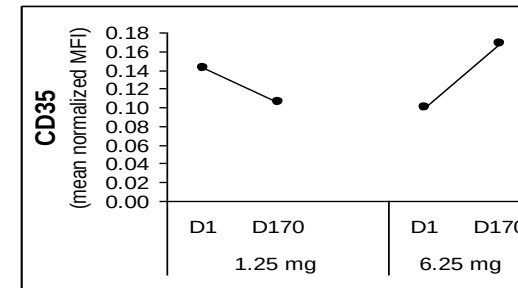
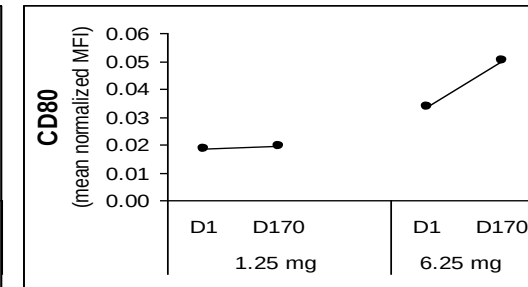
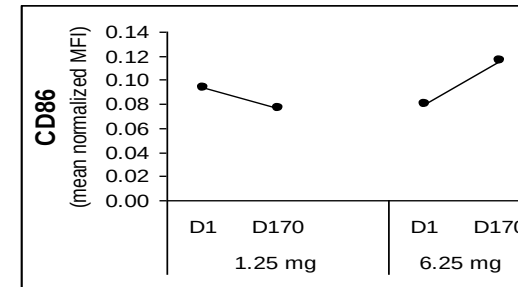
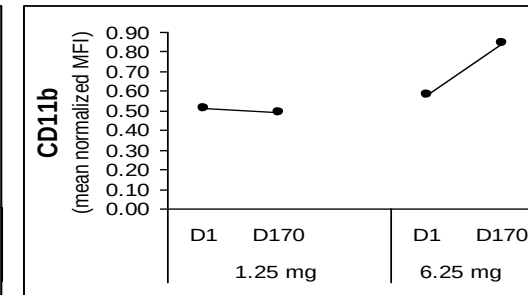
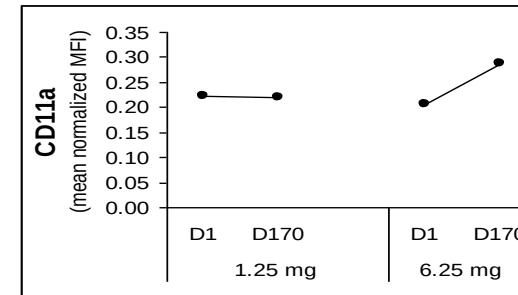


IMP321 in MBC

Completed studies –“Proof of principle”

- 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: all markers are up



AIPAC: a phase IIb in MBC

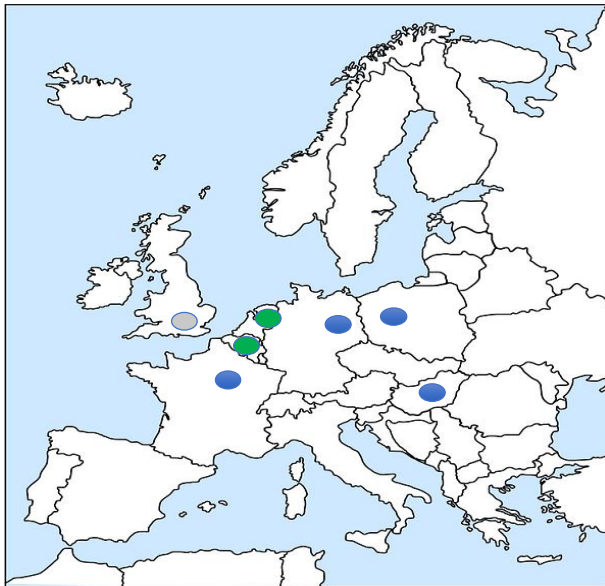


AIPAC (Active Immunotherapy PAClitaxel)

Multinational, multicenter, placebo-controlled, double blind, 1:1 randomized Phase IIb trial in metastatic breast carcinoma patients treated with first-line weekly paclitaxel.

Two stages:

- **Safety run-in stage:** open-label, determining recommended phase two dose (RPTD) of IMP321 in combination with paclitaxel
- **Randomization stage:** IMP321 + paclitaxel vs. paclitaxel + placebo



Features:

- Proof of concept chemo-immunotherapy
- Potential pivotal character (discussed with EMA)
- > 200 pts
- > 30 sites in BE, NL, UK, PL, HU, FR

IMP321 – AIPAC

Design + objectives

Primary objectives:

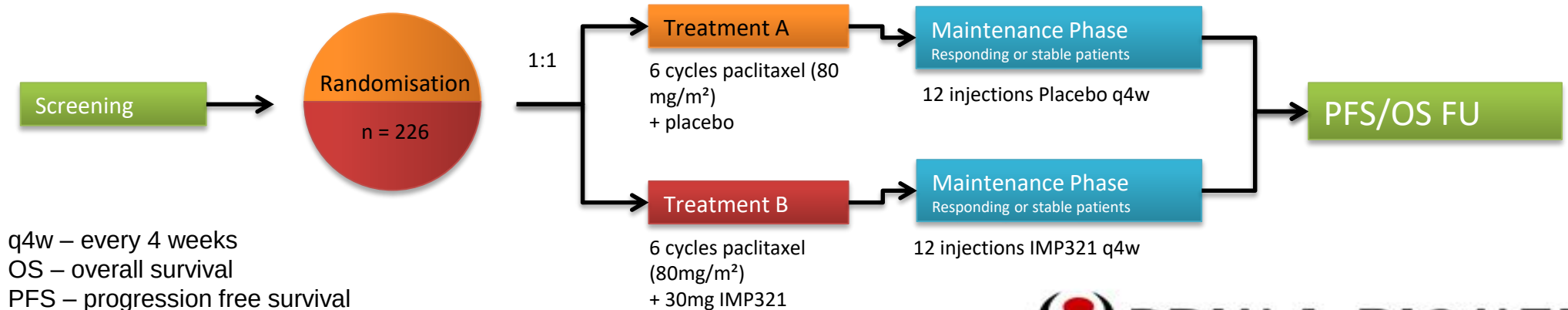
- Safety run-in: recommended phase two dose (RPTD)
- Randomised phase: efficacy of IMP321 + paclitaxel compared to paclitaxel + placebo

Secondary objectives:

- to further characterise the anti-tumour activity of IMP321
- to examine the safety and tolerability of IMP321
- to characterise the pharmacokinetic and immunogenic properties of IMP321
- to assess the quality of life related to IMP321 compared to placebo

Exploratory objectives

- to characterise the immune response of patients and identify biomarkers



Thank you



Frédéric Triebel, CSO/CMO
Precision: Breast Cancer
March 7-8, 2017
Boston, MA.