Combination of paclitaxel and LAG-3Ig (IMP321), a novel MHC class II agonist, as a first-line chemoimmunotherapy in patients with metastatic breast carcinoma (MBC): interim results from the run-in phase of a placebo controlled randomized phase II.

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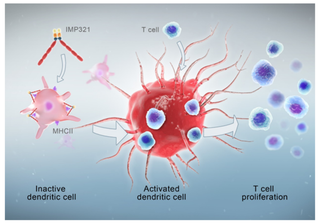
Background



IMP321, a LAG-3Ig fusion protein, is a MHC class II agonist that activates antigen-presenting cell (APC) such as dendritic cells and monocytes (primary pharmacodynamics) and then CD8 T-cells (secondary pharmacodynamics). The activation of the APC network with IMP321 the day after a injection of a single agent chemotherapy may lead to stronger cytotoxic cellular responses associated with an improved long-term Th1 (IFN-γ) immune status, both parameters being essential for a potent immune response against the tumor.

We report here the interim results of the safety run-in stage of the AIPAC trial. The randomisation stage is ongoing.

For more information, please visit:
http://primabiomed.com.au/products/IAG-3.php

Reference: 1 - Brignone et al. Clin Cancer Res 2009;15(19) October 1, 2009
2 - Brignone et al. Journal of Translational Medicine 2010, 8:71
The trial identifiers are IMP321-P011 (sponsor code), 2015-002541-63 (EudraCT) and NCT02614833 (ClinicalTrials.gov).
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Trial design

Multinational, multicenter, placebo-controlled, double blind, 1:1 randomized Phase IIb trial consisting of 2 stages:

- **Safety run-in stage (n = 15)**: open-label, determining recommended phase two dose (RPTD) of IMP321 in combination with weekly paclitaxel for the randomized phase
- **Randomization stage (n = 226):** randomized (1:1), placebo-controlled, double-blind: paclitaxel + IMP321 vs. paclitaxel + placebo

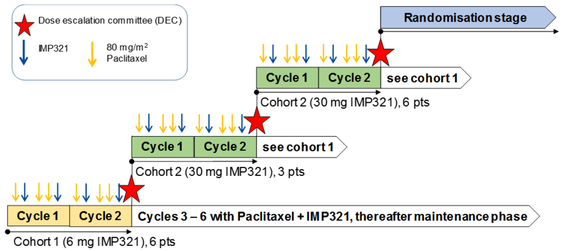
In both stages, treatment consists of a chemo-immunotherapy phase followed by a maintenance phase:

- **chemo-immunotherapy phase**: 6 cycles with weekly paclitaxel (80 mg/m²) at days 1, 8 and 15 + either IMP321 or placebo, on Days 2 and 16 of each 4-week cycle.

- **maintenance phase**: responding or stable patients will receive study agent (IMP321 or placebo) every 4 weeks for additional 12 injections

Dose escalation process

Dose levels of 6 mg and 30 mg IMP321 have been selected based on previous trials with IMP321 in renal cell cancer[1] and metastatic breast cancer[2].



Objectives (safety run-in phase)

Primary:

- To determine the RPTD for the randomised stage

Secondary + Exploratory:

- To determine safety and tolerability
- To assess antitumor activity by best response (RECIST 1.1), PFS and OS
- To characterize the pharmacokinetic properties and immunogenic profile of IMP321
- To evaluate the immune response patients in relation to the treatment with IMP321

Inclusion and exclusion criteria can be found on clinicaltrials.gov (NCT02614833).

Preliminary safety results

In total 15 pts received between 1-18+ IMP321 injections. Cytokine release syndrome grade 1 was the only serious adverse event (SAE) related to IMP321.

Safety parameter	Paclitaxel + 6 mg IMP321 (n=6)	Paclitaxel + 30 mg IMP321, (n=9)	Overall (n=15)
Pts with any AE	6 (100 %)	9 (100 %)	15 (100 %)
Pts with any SAE	5 (83 %)	5 (56 %)	10 (67 %)
No of SAEs	10	7	17
No of SAEs rel. to IMP321	*0*	*2*	*2*
No of SAEs rel. to paclitaxel	*1*	*0*	*1*
Pts with any grade 3/4 AE	5 (83 %)	4 (44 %)	9 (60 %)
Any grade 3/4 AE rel. to IMP321	*0 (0 %)*	*2 (22 %)*	*2 (13 %)*
Any grade 3/4 AE rel. to paclitaxel	*1 (17 %)*	*2 (22 %)*	*3 (20 %)*

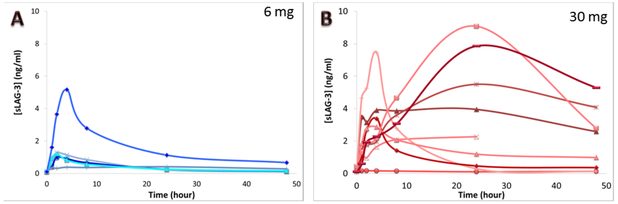
None of the two grade 4 adverse events (AEs) were related to paclitaxel or IMP321. The most common adverse event related to IMP321 were injection site reactions grade 1 and 2 occurring in almost every patient. The dose escalation committee confirmed that 30 mg IMP321 is the recommended phase 2 dose for combination with weekly paclitaxel.

Preliminary efficacy results

The ORR was 47 % accompanied by a DCR of 87 %. Two of the responses occurred relatively late (after ~6 months). Six patients are still on treatment.

Response parameter	Paclitaxel + IMP321 (n = 15)
Complete Response (CR)	0/15 (0 %)
Partial Response (PR)	7/15 (47 %)
Stable Disease (SD)	6/15 (40 %)
Progessive Disease (PD)	2/15 (13 %)
Overall Response Rate (ORR)	7/15 (47 %)
Disease Control Rate (DCR)	13/15 (87 %)

Pharmacokinetics (PK)

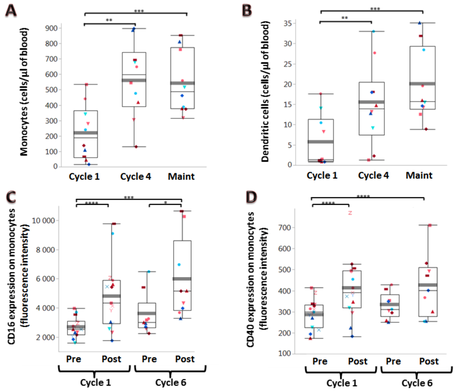


Pharmacokinetic profile of IMP321. A – 6 mg (blue), B – 30 mg (red).
Plasma samples were collected prior to and from 1 to 48 h after the first IMP321 injection of IMP321.

IMP321 shows dose dependent PK profile. Mean C_{max} of 1.7 ng/ml (6 mg IMP321) increases to 4.7 ng/ml at 30 mg. The T_{max} is between 2-4 h and 2-24 h at 6 mg and 30 mg IMP321, respectively.

Primary and secondary pharmacodynamics (PD)

Primary PD: Sustained increase of circulating Antigen-Presenting Cells (APCs) like monocytes (A) and dendritic cells (B). Rapid activation of monocytes (CD16 (C) and CD40 (D)).

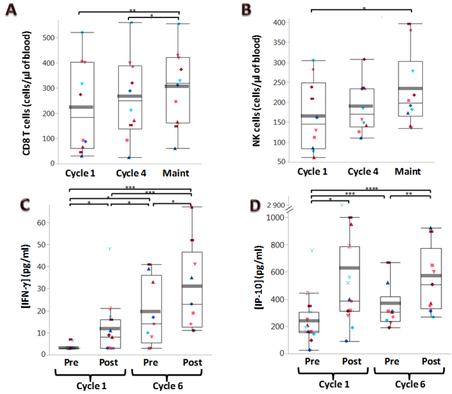


A+B: Samples collected prior to paclitaxel in cycle 1, cycle 4 (i.e. 13 days after 6th IMP321 inj.) and 13 days after the 12th IMP321 inj. (Maint) to monitor the absolute counts of monocytes ($CD45^+CD14^+$) and dendritic cells (Lin- $HLA\text{-}DR^+$ $BDCA\text{-}1/\text{-}2/3^+$).

C+D: Samples collected prior to and 2 days-post 1st IMP321 injection (cycle 1) and 12th IMP321 injection (cycle 6). The expression of activation markers, CD16 (C) and CD40 (D), on $CD45^+CD14^+$ monocytes was analyzed.

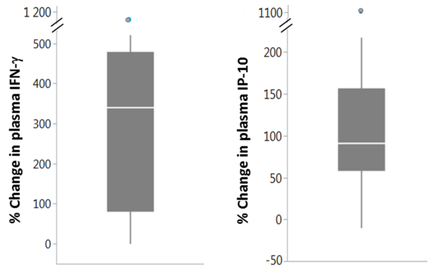
Cohort 1 and 2 are analyzed together (blue = 6 mg; red = 30 mg). The distribution of patients data are shown in box plots: the box indicating 25 % to 75 % quartiles, with the internal line for the median and the whiskers indicating the minimum and maximum values. When applicable, outlier data point are provided. The grey thick line indicates the mean. P values were calculated using the paired t-test: *p < 0.05, **p < 0.01, ***p < 0.005, ****p < 0.001.

Secondary PD: Sustainable increase in absolute numbers of effector cells like i.e. CD8 T cells (A) and Natural Killer cells (B). IMP321 induces early and sustainable increase of Th1 biomarkers like IFN-γ (C) and IP-10 (CXCL10, D).



A+B: Samples collected prior to paclitaxel admin. in cycle 1, cycle 4 (i.e. 13 days after 6th IMP321 inj.) and 13 days after the 12th IMP321 inj. (Maint) to monitor the absolute counts of $CD45^+CD3^+CD8^+CD4^-$ cytotoxic T cells and $CD45^+CD3^-CD16/56^+$ Natural Killer cells.

C+D: Samples collected prior to and from 1 to 48 h after 1st IMP321 injection (cycle 1) and 12th IMP321 injection (at cycle 6)



The baseline (pre-dose) plasma IFN-γ and IP-10 concentrations are increased at cycle 6.

Conclusions

- 30 mg IMP321 is the RPTD in combination with weekly paclitaxel as a first line chemotherapy treatment of MBC
- 6 and 30 mg IMP321 are safe and well tolerated in combination with weekly paclitaxel
- IMP321 in combination with paclitaxel shows encouraging DCR (87 %)
- IMP321 leads to sustainable (> 6 months) increase and activation of APCs (primary PD)
- IMP321 leads to sustainable (> 6 months) increase in CD8 T cell and NK cell numbers, together with an improved pre-dose Th1 status (secondary PD)