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

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Checkpoint blockade: Measures to Enhance Efficacy
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Lymphocyte Activation Gene-3 (LAG-3 or CD223)

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

Genomic LAG-3

Proposed Evolutionary Pattern for LAG-3/CD4

- Duplication of a two Ig domain ancestor

- The LAG-3/CD4 subfamily has evolved like the CTLA-4/CD28 subfamily: one inhibitory and one stimulatory receptor modulating TCR signaling

\[ \text{LAG-3} \quad \text{Co-inhibitory} \]
\[ \text{CD4} \quad \text{Co-stimulatory} \]

*Immunogenetics 39: 213–217, 1994*
Timeline of immune checkpoint discovery.
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
• Functionally similar to CTLA-4 (targeted by Yervoy®) and PD-1 (targeted by Keytruda®)

Positive regulation of antigen presenting cells (APC) → increase in antigen presentation to cytotoxic CD8⁺ T cells

Negative regulation of LAG-3⁺ T cells
Industry increasingly deploying resources to development of LAG-3 technologies...

Increasing Clinical Trials Targeting LAG-3

Sources: GlobalData, company websites, clinical trials.gov, and sec.gov
As of January 2, 2018
Eftilagimod Alpha: an innovative LAG-3 I-O agent

- The only APC targeting LAG-3 product currently in clinical development
- A unique approach (“turning cold tumors into hot tumors” with LAG-3)
- Synergistic with other I-O agents

- LAG-3Ig, an MHC II agonist (eftilagimod alpha): APC activator
  - Boost and sustain the CD8+ T cell responses
  - Activate multiple immune cell subsets

  “pushing the accelerator on immune responses”

- LAG-3 antagonist antibodies: immune checkpoint inhibitor
  - Increase cytotoxicity of the pre-existing CD8 T cell response

  “releasing the brake on the T cell”
Targeting LAG-3 May Lead to Multiple Therapeutics in Numerous Indications

IMMUNOSTIMULATION

- APC
- APC Activator
- Antagonistic mAb
- LAG-3
- T-Cell

Immuno-oncology Combination Therapies
Viral Infections

IMMUNOSUPPRESSION

- Agonistic mAb
- Depleting mAb
- LAG-3
- T-Cell

Rheumatoid Arthritis
IBD
Multiple Sclerosis

(partnered with)
Lead Program
Eftilagimod Alpha (IMP321)
Eftilagimod alpha (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
Eftilagimod alpha (IMP321)
Soluble dimeric recombinant form of LAG-3Ig (fusion protein)

- Highly efficacious in multiple animal models of cancer and infectious disease
- Shown to be safe, non-immunogenic and efficacious in human
IO Therapy Oncology Response Rates

Approximately 70-80% of patients do no respond to anti-PD1 monotherapy. How can we enable more efficacious T-cell responses?

- Immunogenic cell death to liberate/uncover tumor antigens
- Cross-presentation of those antigens
- Recruitment of T cells into the tumor microenvironment
- Reversing the pathways driving a repressive tumor environment

This could be achieved through the right APC activation

APC activators:
- MHC II agonism
- TLR or STING agonism
- CD40 agonism
- Oncolytic viral therapies
Eftilagimod alpha (IMP321)
Induces Better CD8 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 strong IFN+ or IFN+/TNF+ CD8 T cell responses
- Explanation: TLR agonists but not IMP321 induce IL-10 production which suppresses Tc1 differentiation

APC Activation Turns on the Heat on a Cold Tumor (Breast Cancer)

Massive infiltration of T cells (IHC) around the tumor nodules. Some CD3 T cells infiltrating the tumor nodules.

Hemihepatectomy for single residual tumor mass after 13 IMP321 s.c. injections in a MBC patient treated with weekly paclitaxel (AIPAC run-in phase)
Clinical Development
Eftilagimod Alpha (IMP321)
Eftilagimod alpha – 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, antimetabolites, vincas...

• **I-O combination** in various cancer indications
  ➢ With PD-1, PDL-1 or CTLA-4 antagonists...

• **Cancer vaccine or intra-tumoral injections (in situ immunization)**
  ➢ To locally stimulate the immune system
Arm 1, 113 patients: paclitaxel + IMP321

Phase IIb, multinational, randomized, double-blind

Safety run-in: recommended Phase IIb dose (RP2D) Stage 2: Efficacy (PFS)

Primary Objective
Run-In: Recommended Phase II dose (RP2D)
Stage 2: Efficacy (PFS) of paclitaxel + IMP321 vs. paclitaxel + placebo

Other Objectives
Anti-tumor activity, safety and tolerability, pharmacokinetic and immunogenic properties, quality of life of IMP321 plus paclitaxel compared to placebo

Patient Population
Advanced MBC indicated to receive 1st line weekly paclitaxel

Treatment
Run-in: IMP321 (6 or 30 mg) + Paclitaxel
Arm 1: Paclitaxel + IMP321 (30 mg)
Arm 2: Paclitaxel + Placebo

Countries
NL, BE, PL, DE, HU, UK, FR → overall 30+ sites

Status report (Oct 2017)
✓ Safety run-in completed successfully
✓ Randomized phase started early 2017 with the RP2D (30 mg)
✓ Interim-data of safety run-in presented at ASCO 2017
✓ To-date, efficacy and safety data in-line with historical control group/ prior clinical trials (Brignone et al Journal Translational Medicine 2010, 8:71)
✓ Regulatory approval in 7 EU countries
Eftilagimod alpha – Preliminary Efficacy
MBC – 1st line chemotherapy + IMP321

P005 – phase I

AIPAC (P011) – phase I trial

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<tr>
<th>Response parameter</th>
<th>Paclitaxel + IMP321 (n = 15)</th>
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<tr>
<td>Complete Response (CR)</td>
<td>0/15 (0 %)</td>
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<tr>
<td>Partial Response (PR)</td>
<td>7/15 (47 %)</td>
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<tr>
<td>Stable Disease (SD)</td>
<td>6/15 (40 %)</td>
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<td>Progressive Disease (PD)</td>
<td>2/15 (13 %)</td>
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<tr>
<td>Overall Response Rate (ORR)</td>
<td>7/15 (47 %)</td>
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<tr>
<td>Disease Control Rate (DCR)</td>
<td>13/15 (87 %)</td>
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- ORR of 47 % and DCR of 87 %
- Responders had further tumor shrinkage between months 3 and 6
- Compared to historical control groups with 22-33 %, response rates are encouraging
IMP321 leads to sustainable (> 6 months) increase of pre-dose APCs (run-in phase, AIPAC trial).
IMP321 activates APCs (run-in phase, AIPAC trial).
IMP321 leads to sustainable (> 6 months) increase of pre-dose effector CD8 T cells and NK cells (run-in phase, AIPAC trial).
IMP321 leads to sustainable (> 6 months) increase of pre-dose activated (HLA-DR^+ CD38^+) CD4 and CD8 T cells (run-in phase, AIPAC trial).
IMP321 leads to an improved pre-dose Th1 status (IFNγ, IP-10 not shown) (run-in phase, AIPAC trial), a phenomenon not seen with therapeutic anti-PD-1 mAbs.
Eftilagimod Alpha INSIGHT Clinical Trial
Investigator Initiated Trial

**Eftilagimod Alpha in i.t. and i.p. application**
- Prof. Al-Batran, IKF, Frankfurt, Germany
- Population: 18 pts (9 per stratum) with advanced solid tumors w/o standard treatment options
- Objectives: Recommended Phase II dose, PD effects of IMP321
- Design: intrapatient escalation

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<th>Group A: intratumoral (i.t.)</th>
<th>Group B: intraperitoneal (i.p.)</th>
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**Group A:**
- First 3 patients completed escalation w/o DLT,

**Group B:**
- 1\textsuperscript{st} patient completed escalation w/o DLT
Eftilagimod Alpha/Pembrolizumab Combination
Three Groups of Patients Responding to anti-PD-1 (IFN-\(\gamma\) signature)

- A- Inflamed responders – respond to anti-PD-1
- B- Inflamed non-responders (some infiltrates in the tumor margins but no response)
- C- Non inflamed. “Cold tumor” with no response

Optimal checkpoint combos will target groups B and C and help them:
- Promote cross presentation of tumor antigens
- Induce T cell recruitment into tumor microenvironment
Eftilagimod Alpha in Melanoma
TACTI-mel (IO combination)

TACTI-mel trial: Two ACTive Immunotherapeutics in melanoma

- 18 patients, 3 cohorts of 6 patients
- IMP321 + anti-PD-1 (Keytruda®)
- Phase I, multicenter, open label, dose escalation
- Recommended Phase II dose
- Safety and tolerability

**Primary Objective**
Recommended dose for phase II (RP2D) with IMP321 + pembrolizumab
Safety + tolerability

**Other Objectives**
PK and PD of IMP321, response rate, time to next treatment, PFS

**Patient Population**
Unresectable or metastatic melanoma with asymptomatic or suboptimal response after 3 cycles of pembrolizumab

**Treatment**
3 cohorts: 1/6/30 mg IMP321; s.c. q2w + pembrolizumab; starting with the 5th cycle of pembrolizumab

**Status report**
- First dose escalation (1mg → 6mg) successfully confirmed by DSMB in Dec 2016
- Enrolment of cohort 2 (6 mg) completed in Mar 2017
- Interim data presented at SITC 2017
- Full recruitment of 3rd cohort completed in December 2017
  - Data from all 3 cohorts expected mid 2018

6 sites in Australia
Parameter | Patients | %
--- | --- | ---
Disease Control Rate | 8/12 | 66 %
Overall Response Rate | 4/12 | 33 %
Patients with decrease in tumor burden | 7/12 | 58 %

*irPR due to non-target lesions

Safety cohort 1-3:
- In total 114 AEs in 18 patients; thereof 14 AEs >= G3 in 7 pts
- In total 7 SAEs in 6 pts; none related to IMP321 or pembrolizumab
- Related to IMP321: 12 AEs in 9 pts; 1 G3 decreased renal function; 1 G2 rash; rest G1
- Related to Pembro: 35 AEs in 13 pts; 3 G3 in 3 pts (diarrhea, altered liver functions, maculopapular rash)
- No noteworthy abnormalities in lab parameters not coded as AE
Efficacy: metastatic melanoma

All lesions disappeared → CR (confirmed)
patient without treatment but disease free

Preliminary data, status 06th November, 2017
Thank you

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