Activation of the Anti-tumor Immune Responses of γ9δ2 T Cells in Patients with Solid or Hematologic Malignancies with ICT01, a First-in-Class, Monoclonal Antibody Targeting Butyrophilin 3A: The EVICTION Study

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Disclosure Information
A.Marabelle - Over the last 5 years (2016-2021)

INSTITUTIONAL LINKS:

- **Principal Investigator of Clinical Trials from the following companies**: Roche/Genentech, BMS, MSD, Pfizer, Lytxi pharma, Eisai, Astra Zeneca/Medimmune, Tesaro, Chugai, OSE immunotherapeutics, SOTIO, Molecular Partners, Pierre Fabre, Adlai Nortye, Imcheck. **Principal Investigator of the following academic trials**: ACSE NIVOLUMAB/NCT03012581 (funding INCa, Ligue contre le Cancer & BMS; sponsor Unicancer), ISI/JX/NCT02977156 (funding Transgene; sponsor Leon Berard Cancer Center), NIVIPIIT/NCT02857569 (funding BMS; sponsor Gustave Roussy), PEMBIB/NCT02856425 (funding Boehringer Ingelheim; sponsor Gustave Roussy). **Sub-Investigator of Clinical Trials sponsored by the following companies**: Aduro Biotech, Agios Pharmaceuticals, Amgen, Argen-X Bvba, Arno Therapeutics, Astex Pharmaceuticals, Astra Zeneca, Aveo, Bayer Healthcare Ag, Bbb Technologies Bv, Biogene, Bioalliance Pharma, Biocentec Ag, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Ca, Celgene Corporation, Chugai Pharmaceutical Co., Clovis Oncology, Daiichi Sankyo, Debiopharm S.A., Eisai, Exelixis, Forma, Gamamabs, Genentech, Inc., Gilead Sciences, Inc, Glaxosmithkline, Glenmark Pharmaceuticals, H3 Biomedicine, Inc, Hoffmann La Roche Ag, Incyte Corporation, Innate Pharma, Iris Servier, Janssen , Kura Oncology, Kyowa Kirin Pharm, Lilly, Loxo Oncology, Lytxi Biopharma As, Medimmune, Menarini Ricerche, Merck Sharp & Dohme Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Nanobodies, Nektar Therapeutics, Novartis Pharma, Octitrem Oncology Nv, Oncoethix, Oncomed, Oncopeptides, Onyx Therapeutics, Orion Pharma, Onyxon Genomics, Pfizer, Pharma Mar, Pierre Fabre , Rigontec Gmbh, Roche, Sanofi Aventis, Sierra Oncology, Taiho Pharma, Tesaro, Inc, Tioma Therapeutics, Inc., Xencor. **Gustave Roussy Research Grants**: AstraZeneca, BMS, Boehringer Ingelheim, Janssen Cilag, Merck, Novartis, Pfizer, Roche, Sanofi. **Non-Financial Support (drug supply to Gustave Roussy sponsored trials)**: Astra Zeneca, Bayer, BMS, Boehringer Ingelheim, Johnson & Johnson, Lilly, Medimmune, Merck serono, NH TherAGuX, Pfizer, Roche.

PERSONAL LINKS:

- **Member of Clinical Trial Scientific Advisory Boards**: Innate Pharma, Merck Serono, eTheRNA, Lytxi pharma, Kyowa Kirin Pharma, Bayer, Novartis, BMS, Symphogen, Genmab, Amgen, Biothera, Nektar, GS, Oncovir, Pfizer, Seattle Genetics, Roche/Genentech, OSE immunotherapeutics, Transgene, Grifiti, Merck (MSD), Cerenis, Protagen, Partner Therapeutics, Servier, Sanofi, Pierre Fabre, Molecular Partners, IMCheck, Medicix, Takeda, EISAI, HiFiBio, RedX, J&J, Gilead, Alkermes, Medincell. **Teaching/Speaker Bureau activities**: Roche/Genentech, BMS, Merck (MSD), Merck Serono, Astra Zeneca/Medimmune, Amgen, Sanofi. **Scientific & Medical Consulting**: Roche, Pierre Fabre, Onxeo, EISAI, Bayer, Genticel, Rigontec, Daiichi Sankyo, Sanofi, BioNTech, Corvus, GLG, Deerfield, Guidepoint Global, Edmark, System Analytics, imCheck, Sotio, Bioncotech, Molecular Partners, Pillar Partners, Boehringer Ingelheim, T3 Pharma, Servier, Takeda, GI Innovation, Medincell. **Non-Financial Support (travel expenses)**: Astra Zeneca, BMS, Merck (MSD), Roche. **Co-Founder & Share Holder**: PEGASCY SAS (Gustave Roussy Spin Off for Drug Repositioning); Centessa Pharmaceuticals; Share Holder; HiFiBio, Shattuck Labs. **Patent Issued (not licensed yet)**: "Monoclonal Antibodies to CD81", Stanford Office of Technology Licensing, 3000 El Camino Real, Bldg. 5, Suite 300, Palo Alto, CA 94306-2100. U.S. Application Serial No. 62/351,054. **Pre-Clinical and Clinical Research Grants (Institutional Funding)**: Merus, BMS, Boehringer Ingelheim, Transgene, Fondation MSD Avenir. **Member of the following scholar societies**: European Society for Medical Oncology (ESMO), American Society for Clinical Oncology (ASCO), American Association for Cancer Research (AACR), European Academy for Tumor Immunology (EATI), Founder and president of the French society for Immunotherapy of Cancer (FITC). **Member of the board of the Immuno-Oncology Group at the French Network of Comprehensive Cancer Centers (Unicancer).** Member of the working group on rheumatic adverse events induced by cancer immunotherapies of the European League Against Rheumatoid Arthritis (EULAR). **Supervisory Board Member** of the Gustave Roussy Foundation. **Member of the Steering Committee** of the Immuno-Oncology Task Force at Unicancer. **Member of the editorial boards of** the European Journal of Cancer and ESMO IO Tech.
Rationale for Targeting $\gamma^9\delta^2$ T Cells through Butyrophilin (BTN) 3A

A. $\gamma\delta$ T cells infiltrate into most solid & liquid tumors

B. Strongest correlation with favorable prognosis of all TILs

C. BTN3A is stress signal recognized by $\gamma^9\delta^2$ T cells

D. BTN3A Isoforms are overexpressed in multiple cancers

ICT01 MoA: a First-in-Class anti-BTN3A mAb which triggers the Anti-Tumor Activity of $\gamma\delta^2$ T Cells

1. In vivo $\gamma\delta^2$ T cell activation & trafficking in <30 min
2. Cytokine Production & Immune Activation
   - IFN-$\gamma$ & TNF-$\alpha$ release

3. Cytotoxicity
   - Granzyme B & Perforin release

ICT01 binding $\rightarrow$ BTN3A1/2/3 active conformation (stress mimicking mechanism)

- 1. Activation & Trafficking
- 2. Cytokine Production & Immune Activation
- 3. Cytotoxicity

Cytotoxicity requires 2nd signal (e.g., NKG2D-MICA) to activated $\gamma\delta^2$ T cells from stressed/malignant/infected cell

Cytokines

- TNF-$\alpha$ Secretion
- IFN-$\gamma$ Secretion
- CD25 + (% among V$\delta$2 T cells)

Cytokine Production & Immune Activation

- TNF-$\alpha$ Secretion
- IFN-$\gamma$ Secretion
- CD25 + (% among V$\delta$2 T cells)

Surface CD25

- TNF-$\alpha$ Secretion
- IFN-$\gamma$ Secretion
- CD25 + (% among V$\delta$2 T cells)

Tissue homing

- TNF-$\alpha$ Secretion
- IFN-$\gamma$ Secretion
- CD25 + (% among V$\delta$2 T cells)

Migration into tumors

Pro-Inflammatory TME

Cancer Cell Killing

ICT01 (ug/ml)

% of Live cells (relative to untreated)

- PC3
- HT29
- HCT116
- MDAMB231
- SW620
- DU145

Concentration (µg/ml)

- JURKAT
- THP1
- HL60
- K562
- RAJI
- DAUDI
- Molm 14

0.01 0.1 1 10 100

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Concentration (µg/ml)
EVICION Trial Design of ICT01 as Monotherapy and in Combination with Pembrolizumab (anti-PD1)

Part 1 Indication Selection:
1. BTN3A expressing tumors
2. γδ T cell infiltrating tumors

Main Eligibility Criteria:
1. M/F >18 yrs of age
2. No remaining standard of care
3. ECOG ≤ 1
4. Life expectancy > 3 mos
5. Willing to undergo biopsy
6. Pembro combo: must have been eligible per approved label

Participating Countries/Sites:
France, Belgium, Germany, Spain, UK and US
## Patient Characteristics and Adverse Events

### Group A Solid Tumor ICT01 Monotherapy

<table>
<thead>
<tr>
<th>Cohort 1 20-700 mcg</th>
<th>Diagnosis</th>
<th>Age (Sex)</th>
<th>Average # Prior CA Regimens (Range)</th>
<th>Possibly/Related AEs (n=1 unless specified)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRC x 3 Melanoma, Ovarian, PDAC</td>
<td>41-67 yo 4M/2F</td>
<td>5.6 (2-8)</td>
<td>Fever (2), Rash, Arthralgia, N/V</td>
</tr>
<tr>
<td>Cohort 2 2 mg</td>
<td>CRC x 3 Melanoma x 2</td>
<td>28-66 yo 5M</td>
<td>4.4 (2-6)</td>
<td>Fever (3), Chills, Fatigue, Elevated CRP</td>
</tr>
<tr>
<td>Cohort 3 7 mg</td>
<td>Breast x 2 PDAC, Gastric</td>
<td>50-66 yo 1M/3F</td>
<td>6.5 (3-11)</td>
<td>Fever, Chills, N/V, Asthenia</td>
</tr>
<tr>
<td>Cohort 4 20 mg</td>
<td>Bladder, CRC Ovarian, PDAC Prostate</td>
<td>42-74 yo 4M/1F</td>
<td>5.8 (2-9)</td>
<td>Fever (4*), N/V, Shivers</td>
</tr>
</tbody>
</table>

### Group B Hematologic Malignancies ICT01 Monotherapy

<table>
<thead>
<tr>
<th>Cohort 1 700 mcg</th>
<th>Diagnosis</th>
<th>Age (Sex)</th>
<th>Average # Prior CA Regimens (Range)</th>
<th>Possibly/Related AEs (n=1 unless specified)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AML x 2 FL</td>
<td>71-73 yo 1M/2F</td>
<td>4.3 (4-5)</td>
<td>Asthenia, Neutropenia, Vertigo, Tremor</td>
</tr>
</tbody>
</table>

*Only patient without fever had 0 g9d2 T cells at baseline

**AE Summary:**
- Transient 1st dose fever is most common AE (all Grade 1 or 2); frequency generally increasing with dose
- No safety concerns/signals or DLTs identified allowing dose escalation to continue
ICT01 Exposure and Target Occupancy

**ICT01 Rapidly Binds BTN3A in a Dose Dependent Manner**

### A. ICT01 Dose-dependent Exposure

- **2 mg**
- **7 mg**
- **20 mg**

Rapid initial distribution following IV infusion followed by a slower elimination phase consistent with mAbs.

### B. Target Occupancy: Available BTN3A

Note: ~20% TO *in vitro* = EC$_{90}$ for tumor killing.
Single & Multiple IV Doses of ICT01 Induce Rapid Activation & Trafficking of $\gamma 9\delta 2$ T Cells (Cohort means)

1. Doses $\geq 70$ $\mu$g led to rapid, selective activation of $\gamma 9\delta 2$ T cells <30 mins post dose
2. The majority of activated $\gamma 9\delta 2$ T cells migrated out of the circulation within 30 min post dose
3. Activation and migration of $\gamma 9\delta 2$ T cells were observed post 2$^{nd}$ & 3$^{rd}$ doses

**A. Activation (% of CD69+$\gamma 9\delta 2$ T Cells)**

**B. $\gamma 9\delta 2+$ T Cell Trafficking (% Baseline)**
ICT01 Also Impacts the Homing of CD8 T & NK Cells
Effects likely secondary to γ9δ2 T cell activation and cytokine secretion

Granulocytes

Monocytes

B Cells

T Cells

CD4 T Cells

CD8 T Cells

NK Cells

A4_20 mg (n=4)
A3_7 mg (n=4)
A2_2 mg (n=5)
A1_700/700 ug (n=2)
A1_200 ug (n=2)
A1_70/700 ug (n=1)
ICT01 Monotherapy or in Combination with Pembro Produce Similar PD Effects on γ9δ2 T Cells (700μg)

**ICT01, Alone Hematologic CA**

- **Target Occupancy**
  - % Free Receptor (nM20.1)
  - Days: 0, 20, 30

- **γ9δ2 T cells Number and Frequency**
  - VγδV2 T cells (cells/ml)
  - Days: 0, 20, 30
  - % VγδV2 T cells (among lymphocytes)
  - Days: 0, 20, 30

- **γ9δ2 TCell Activation**
  - % CD95+
  - Days: 0, 20

  - ID 0102012 (AML)
  - ID 0103002 (AML)
  - ID 0103003 (AML)

25 to 40% TO @ 30 min
60-80% decrease of circulating γ9δ2 T cells
Signs of acute activation

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**Pembro Combo Solid Tumors**

- **Target Occupancy**
  - % Free Receptor (nM20.1)
  - Days: 0, 20, 30

- **γ9δ2 T cells number and frequency**
  - VγδV2 T cells (cells/ml)
  - Days: 0, 20, 30
  - % VγδV2 T cells (among lymphocytes)
  - Days: 0, 20, 30

- **γ9δ2 T activation**
  - % CD95+
  - Days: 0, 20

  - ID 0401009 (NSCLC)
  - ID 0401011 (NSCLC)
  - ID 0102010 (Bladder)

20-55% TO @ 30 min
60-90% decrease of circulating γ9δ2 T cells
Signs of acute activation
Circulating IFNγ and TNFα Levels Increase Post ICT01 Group A, Relationship to Baseline γ9δ2 T Cell Counts

- IFNγ and TNFα are the 2 main cytokines produced by activated γ9δ2 T cells
- Serum samples were collected at 0.5, 4 and 24 hours post first dose of ICT01
- Maximum levels were observed at 4 hours post dose and used for correlation analysis

Summary
1. Trend for linear correlation between Vγ9δ2 T cell levels at baseline and circulating IFNγ and TNFα
2. ICT01 Dose-response for IFNγ; less apparent for TNFα
ICT01 Increases Intra-tumor Immune Cell Density

41-yo female with Metastatic Melanoma (70/700 μg ICT01)

Digital Pathology: automated cell counts per mm² of tumor conducted at HalioDx (Marseille, France)
ICT01 Increases Intra-tumor Immune Cell Density

57-yr male with Gastric cancer (7 mg ICT01)

Pre-Treatment

Day 28

Fresh frozen tumor biopsy

Formalin-fixed paraffin-embedded tumor biopsy

**Vg9 TCR+ Cells**

- Pre-Treatment
- Day 28

**pan-γδ TCR+ T Cells**

- Pre-Treatment

**CD3+ T Cells**

- Pre-Treatment

**CD8+ T Cells**

- Pre-Treatment

Digital Pathology: automated cell counts per mm² of tumor conducted at HalioDx (Marseille, France)

Summary of EVICTION Trial Safety and Pharmacodynamic Activity Data

1. Safety and tolerability have been good at ICT01 doses up to 75mg
2. ICT01 activates circulating $\gamma 9\delta 2$ T cells through targeting of BTN3A, which results in rapid migration from the circulation
3. Activation of $\gamma 9\delta 2$ T cells results in increases in IFN$\gamma$ and possibly TNF$\alpha$ levels that appear to have downstream effects that lead to activation of NK and CD8 T cells at higher ICT01 doses
4. Upon ICT01 treatment, increases in $\gamma \delta$, CD3 and CD8 T cell densities are observed in tumor biopsies, which supports the hypothesis of an expanded anti-tumor immune response following $\gamma 9\delta 2$ T cell targeting
Thanks to participate to the Eviction trial

- To the patients and their families
- To the investigators, study nurses and site staff
- To the ICT01 Clinical Advisory Board
- To the Imcheck team