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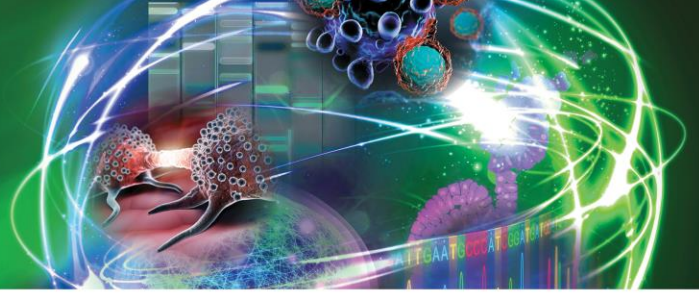

Activation of the Anti-tumor Immune Responses of γ9δ2 T Cells in Patients with Solid or Hematologic Malignancies with ICT01, a First-in-Class, Monoclonal Antibody Targeting Butyrophilin 3A: The EVICTION Study

Aurélien Marabelle, MD, PhD
Gustave Roussy
INSERM U1015 & CIC1428
Université Paris Saclay
Villejuif, France

Disclosure Information

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

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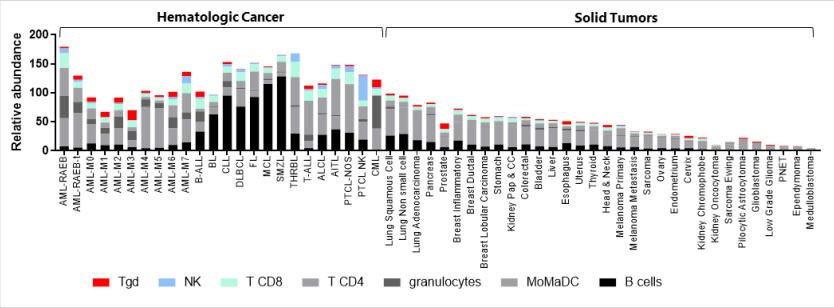
- **INSTITUTIONAL LINKS:**
- **Principal Investigator of Clinical Trials from the following companies:** Roche/Genentech, BMS, MSD, Pfizer, Lytix pharma, Eisai, Astra Zeneca/Medimmune, Tesaro, Chugai, OSE immunotherapeutics, SOTIO, Molecular Partners, Pierre Fabre, Adlai Nortye, Imcheck. **Principal 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), NIVIPIT/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, Beigene, Bioalliance Pharma, Biontech 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, Lytix Biopharma As, Medimmune, Menarini Ricerche, Merck Sharp & Dohme Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Octimet Oncology Nv, Oncoethix, Oncomed, Oncopeptides, Onyx Therapeutics, Orion Pharma, Oryzon 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 TherAGuiX, Pfizer, Roche.

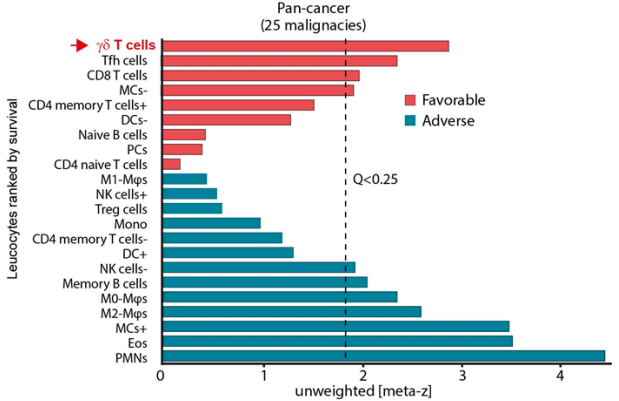
- **PERSONAL LINKS:**
- **Member of Clinical Trial Scientific Committee:** NCT02528357 (GSK), NCT03334617 (Astra Zeneca). **Member of Data Safety and Monitoring Board:** NCT02423863 (Oncovir, Inc.). **Scientific Advisory Boards :** Innate Pharma, Merck Serono, eTheRNA, Lytix pharma, Kyowa Kirin Pharma, Bayer, Novartis, BMS, Symphogen, Genmab, Amgen, Biothera, Nektar, GSK, Oncovir, Pfizer, Seattle Genetics, Roche/Genentech, OSE immunotherapeutics, Transgene, Gritstone, Merck (MSD), Cerenis, Protagen, Partner Therapeutics, Servier, Sanofi, Pierre Fabre, Molecular Partners, IMCheck, Medicxi, 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, Daichii Sankyo, Sanofi, BioNTech, Corvus, GLG, Deerfield, Guidepoint Global, Edimark, 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 Rhumatoid 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 γ9δ2 T Cells through Butyrophilin (BTN) 3A

A. γδ T cells infiltrate into most solid & liquid tumors

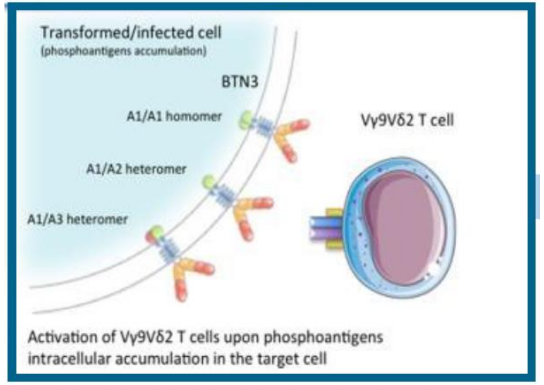


B. Strongest correlation with favorable prognosis of all TILs

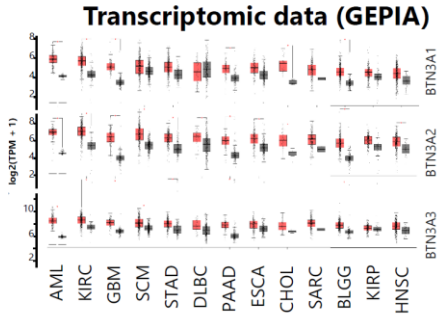


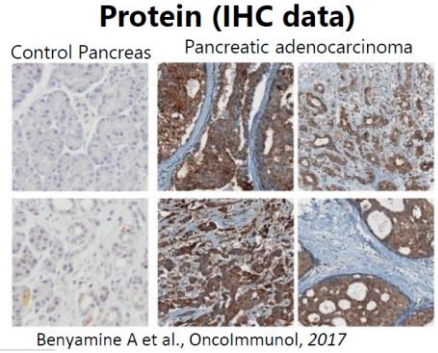
Adapted from Tosolini et al, OncoImmunol, 2017 and Gentles et al, Nat Med, 2015

C. BTN3A is stress signal recognized by γ9δ2 T cells



D. BTN3A Isoforms are overexpressed in multiple cancers





Benyamine A et al., OncoImmunol, *2017*

ICT01 MoA: a First-in-Class anti-BTN3A mAb which triggers the Anti-Tumor Activity of γ9δ2 T Cells

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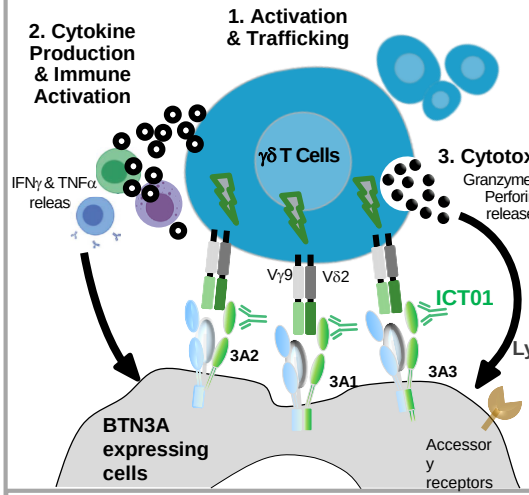
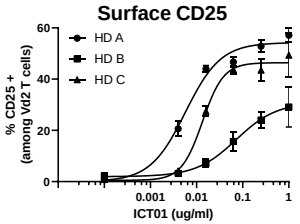
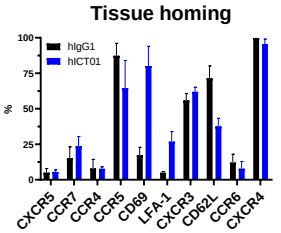
ICT01 binding ➔ BTN3A1/2/3 active conformation
(stress mimicking mechanism)



1. In vivo γ9δ2 T cell activation & trafficking in <30 min
2. Cytokines lead to activation of other immune cells, incl αβ T Cells, APCs, & B cells
3. Cytotoxicity requires 2nd signal (e.g., NKG2D-MICA) to activated γ9δ2 T cells from stressed/malignant/infected cell

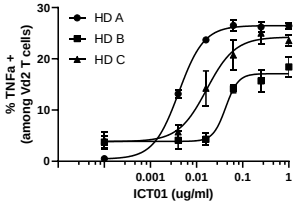
Activation

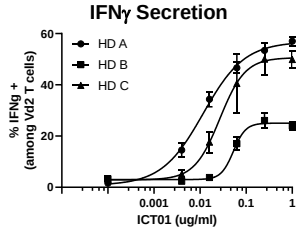




Migration into tumors

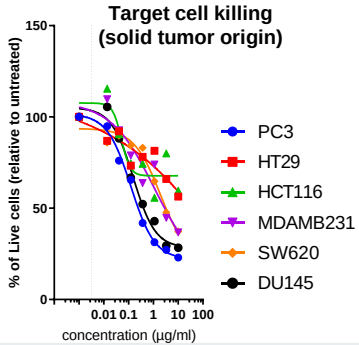
Cytokines

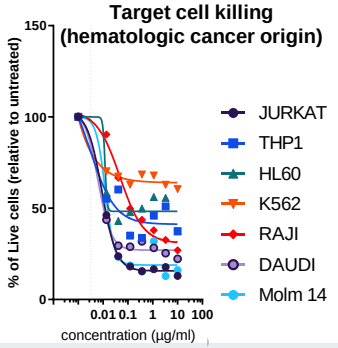




Pro-Inflammatory TME

Cytotoxicity





Cancer Cell Killing

EVICTION Trial Design of ICT01 as Monotherapy and in Combination with Pembrolizumab (anti-PD1)

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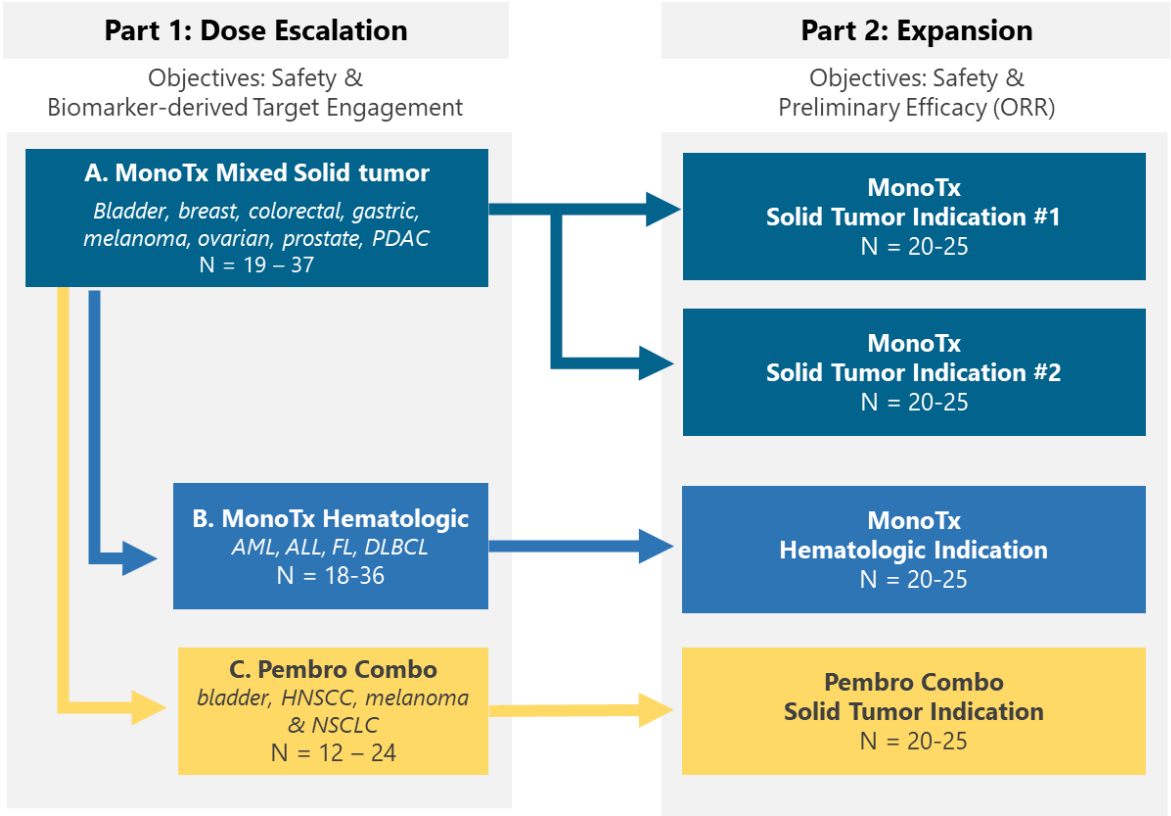


Part 1 Indication Selection:

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

	Diagnosis	Age Sex	Average # Prior CA Regimens (Range)	Possibly/Related AEs (n=1 unless specified)
Group A Solid Tumor ICT01 Monotherapy				
Cohort 1 20-700 mcg	CRC x 3 Melanoma, Ovarian, PDAC	41-67 yo 4M/2F	5.6 (2-8)	Fever (2), Rash, Arthralgia, N/V
Cohort 2 2 mg	CRC x 3 Melanoma x 2	28-66 yo 5M	4.4 (2-6)	Fever (3), Chills, Fatigue, Elevated CRP
Cohort 3 7 mg	Breast x 2 PDAC, Gastric	50-66 yo 1M/3F	6.5 (3-11)	Fever, Chills, N/V, Asthenia
Cohort 4 20 mg	Bladder, CRC Ovarian, PDAC Prostate	42-74 yo 4M/1F	5.8 (2-9)	Fever (4*), N/V, Shivers
Group B Hematologic Malignancies ICT01 Monotherapy				
Cohort 1 700 mcg	AML x 2 FL	71-73 yo 1M/2F	4.3 (4-5)	Asthenia, Neutropenia, Vertigo, Tremor

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

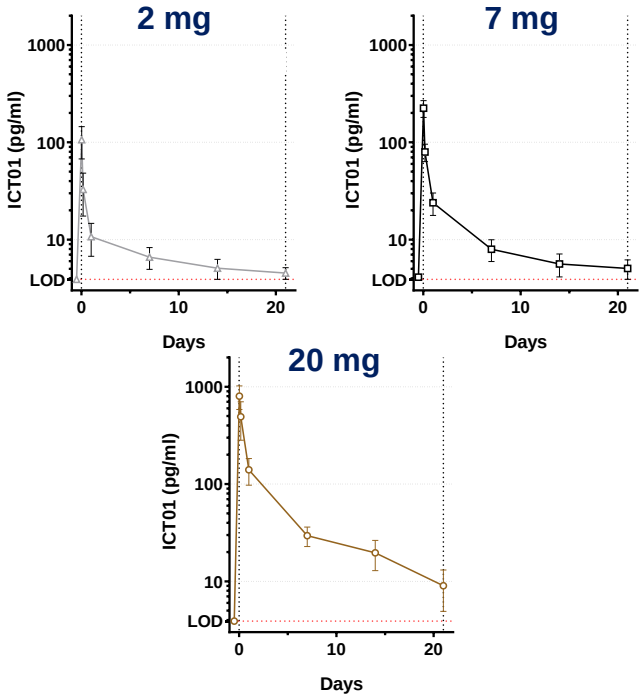
AE Summary:

- 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

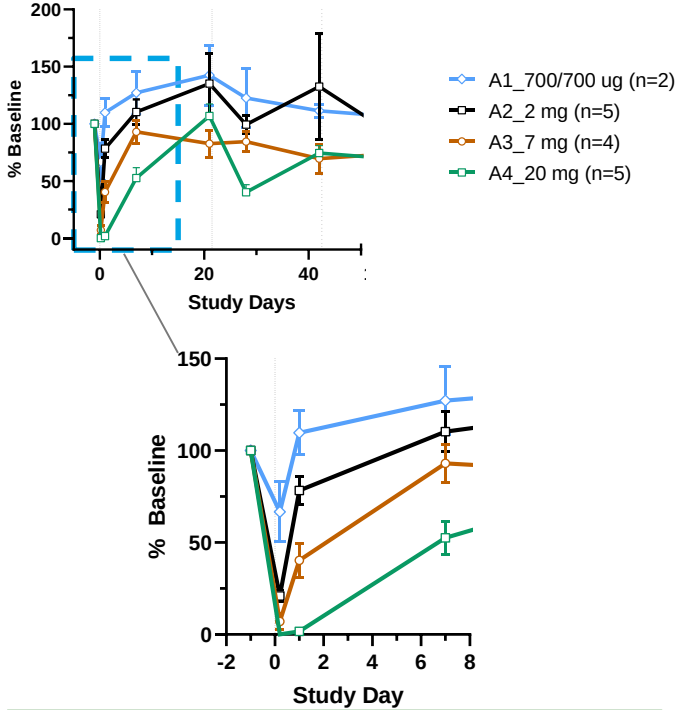
ICT01 Rapidly Binds BTN3A in a Dose Dependent Manner

A. ICT01 Dose-dependent Exposure



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 γ9δ2 T Cells (Cohort means)

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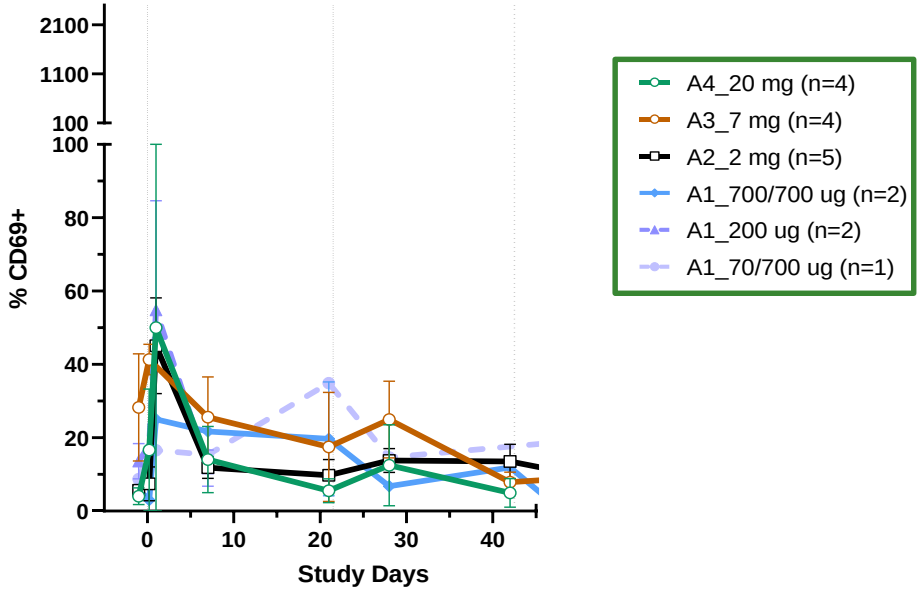
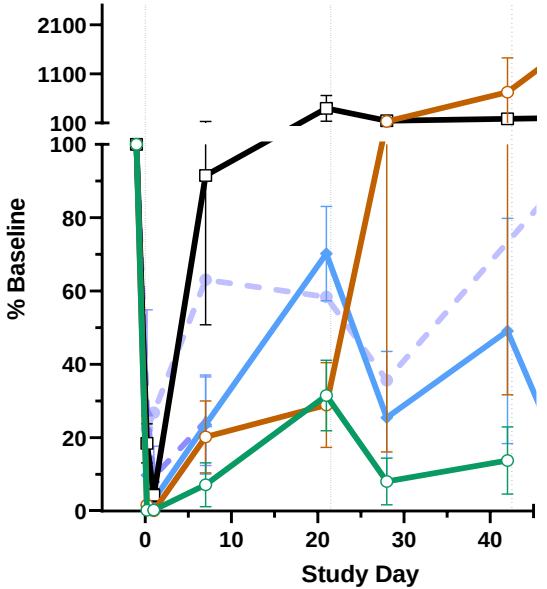
A. Activation (% of CD69+γ9δ2 T Cells)



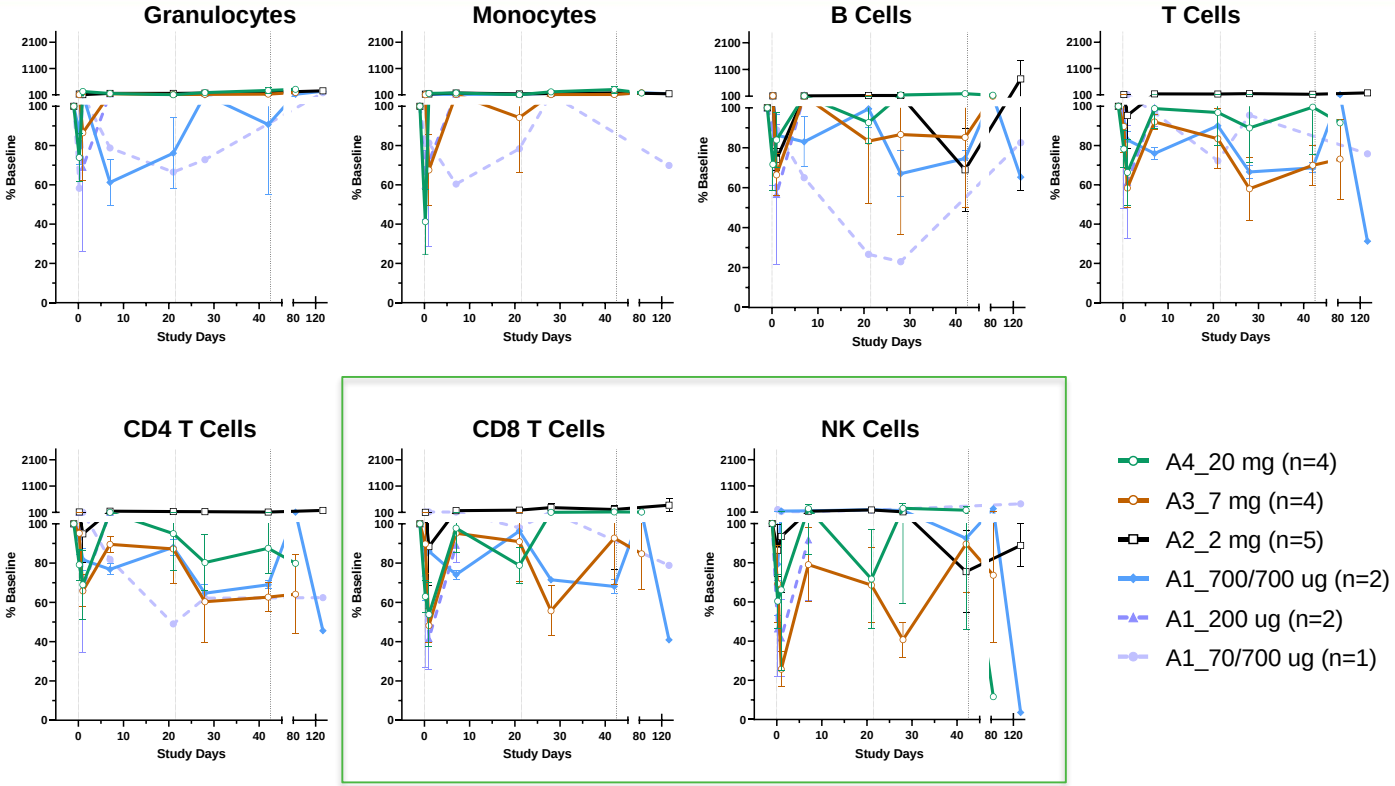
B. γ9δ2+ T Cell Trafficking (% Baseline)



1. Doses ≥70 μg led to rapid, selective activation of γ9δ2 T cells <30 mins post dose
2. The majority of activated γ9δ2 T cells migrated out of the circulation within 30 min post dose
3. Activation and migration of γ9δ2 T cells were observed post 2nd & 3rd doses

ICT01 Also Impacts the Homing of CD8 T & NK Cells

Effects likely secondary to γ9δ2 T cell activation and cytokine secretion



ICT01 Monotherapy or in Combination with Pembro Produce Similar PD Effects on γ9δ2 T Cells (700μg)

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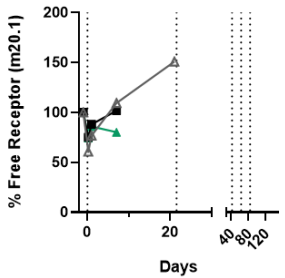
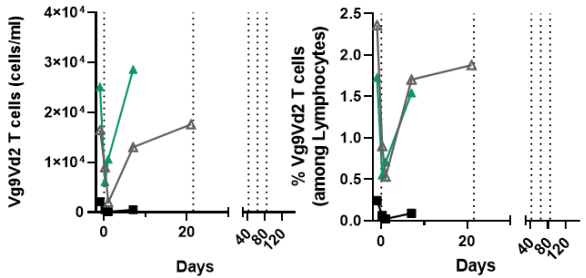
ICT01 Alone Hematologic CA

Target Occupancy



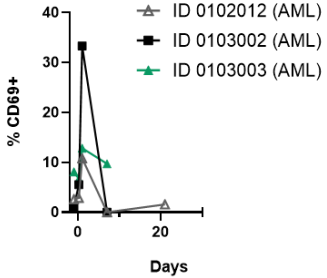
25 to 40% TO @ 30 min

γ9δ2 T cells Number and Frequency



60-80% decrease of circulating γ9δ2 T cells

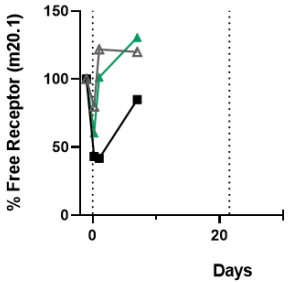
γ9δ2 T Cell Activation



Signs of acute activation

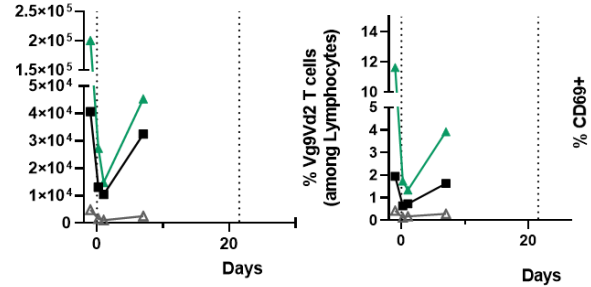
Pembro Combo Solid Tumors

Target Occupancy



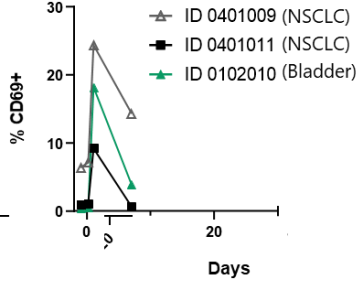
20-55% TO @ 30 min

γ9δ2 T cells number and frequency



60-90% decrease of circulating γ9δ2 T cells

γ9δ2 T activation

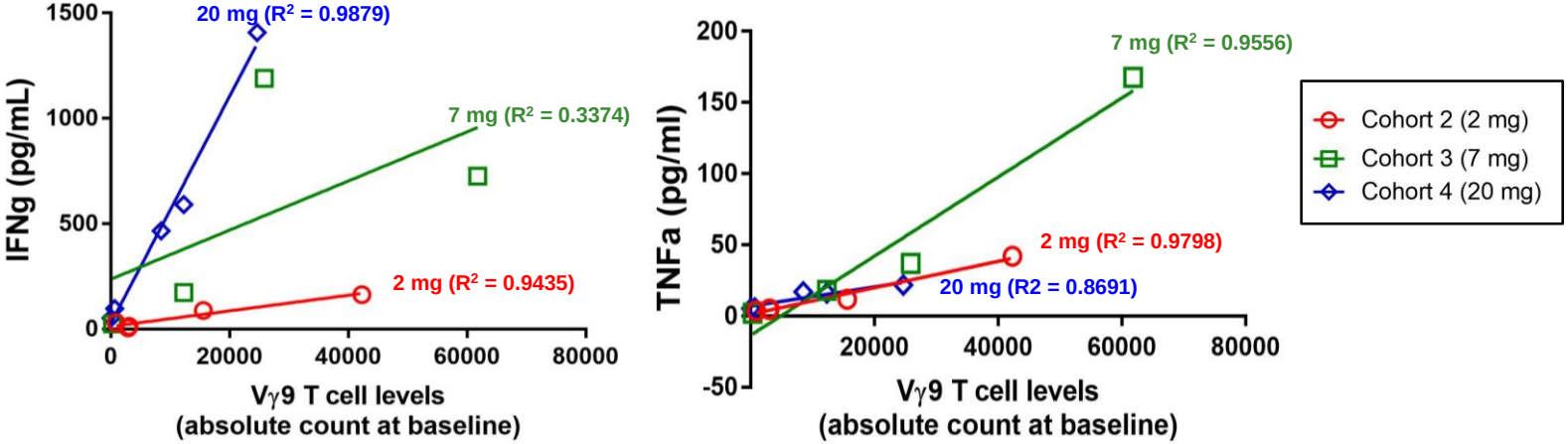


Signs of acute activation

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



Serum cytokines were batch analyzed by dose cohort at Precision for Medicine (Berlin, Germany) using a validated MSD 10-plex panel,.

Summary

1. Trend for linear correlation between Vγ9d2 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)

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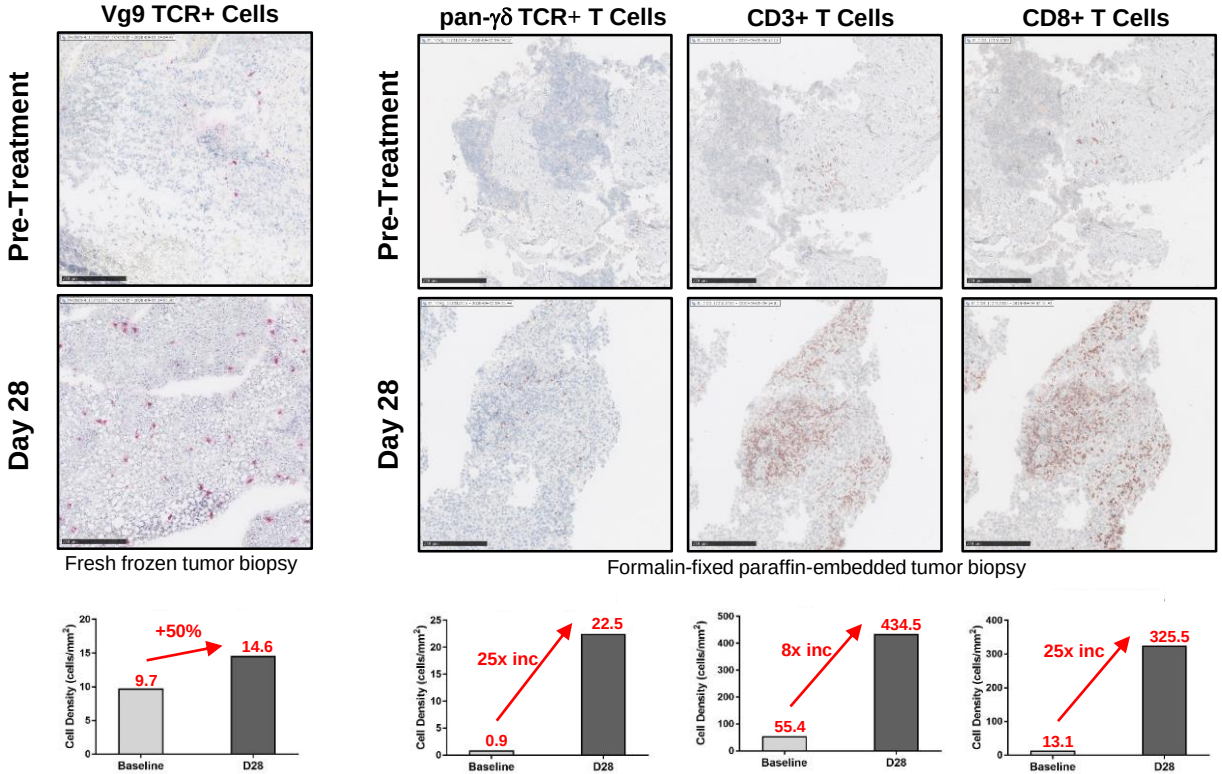

Digital Pathology: automated cell counts per mm² of tumor conducted at HalioDx (Marseille, France)

ICT01 Increases Intra-tumor Immune Cell Density

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

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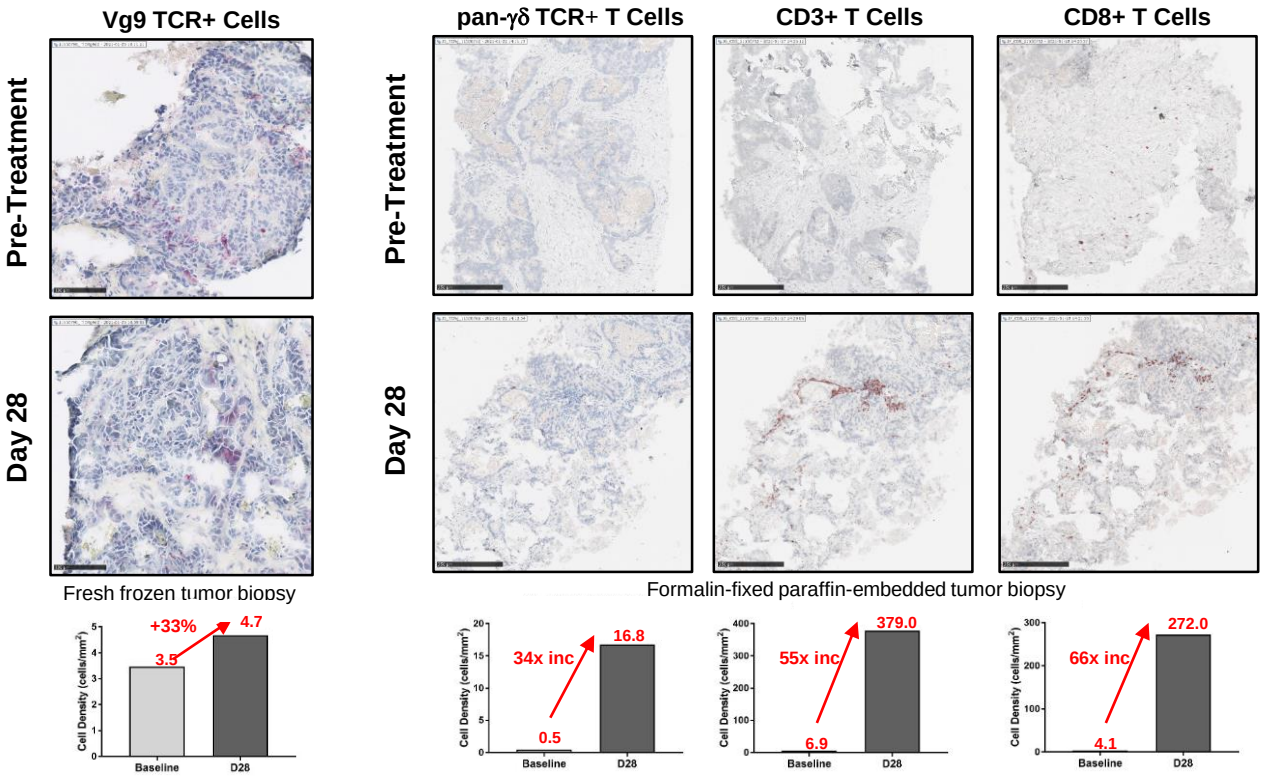

Digital Pathology: automated cell counts per mm² of tumor conducted at HalioDx (Marseille, France)

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 γ9δ2 T cells through targeting of BTN3A, which results in rapid migration from the circulation
3. Activation of γ9δ2 T cells results in increases in IFNγ and possibly TNFα 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 γδ, CD3 and CD8 T cell densities are observed in tumor biopsies, which supports the hypothesis of an expanded anti-tumor immune response following γ9δ2 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