2021 ESMO congress

Coordinated Activation of Antitumor Responses of γ9δ2 and CD8 T Cells by Targeting BTN3A with ICT01 in Patients with Solid Tumors: EVICTION Trial

Abstract 958O (ID4530)

Prof Aurélien Marabelle, MD, PhD
Gustave Roussy, Paris, France

Aurélien Marabelle, Martin Wermke, Christiane Jungels, Johann de Bono, Norbert Vey, Elena Garralda, Steven Le Gouill, Patricia LoRusso, Aude De Gassart, Patrick Brune, Emmanuel Valentin, Marina Iché, Daniel Olive, Paul A. Frohna

DECLARATION OF INTERESTS

Aurélien MARABELLE, MD, PhD / PAST 5 YEARS DISCLOSURES

Scientific Advisory Boards : Merck Serono, eTheRNA, Lytix pharma, Kyowa Kirin Pharma, Novartis, BMS, Symphogen, Genmab, Amgen, Biothera, Nektar, Tesaro/GSK, Oncosec, Pfizer, Seattle Genetics, Astra Zeneca/Medimmune, Servier, Gritstone, Molecular Partners, Bayer, Partner Therapeutics, Sanofi, Pierre Fabre, RedX pharma, OSE Immunotherapeutics, Medicxi, HiFiBio, IMCheck, MSD, iTeos, Innate Pharma, Shattuck Labs, Medincell, Tessa Therapeutics, PegaOne.

Teaching/Speaker activities: Roche/Genentech, BMS, Merck (MSD), Merck Serono, Astra Zeneca/Medimmune, Amgen, Sanofi, Servier.

Scientific & Medical Consulting : Roche, Pierre Fabre, Onxeo, EISAI, Bayer, Genticel, Rigontec, Daichii Sankyo, Imaxio, Sanofi/BioNTech, Molecular Partners, Pillar Partners, BPI, Faron, Applied Materials.

Non-Financial Support (travel expenses): Astra Zeneca, BMS, Merck (MSD), Roche.

Shareholder: Centessa Pharmaceuticals, Shattuck Labs.

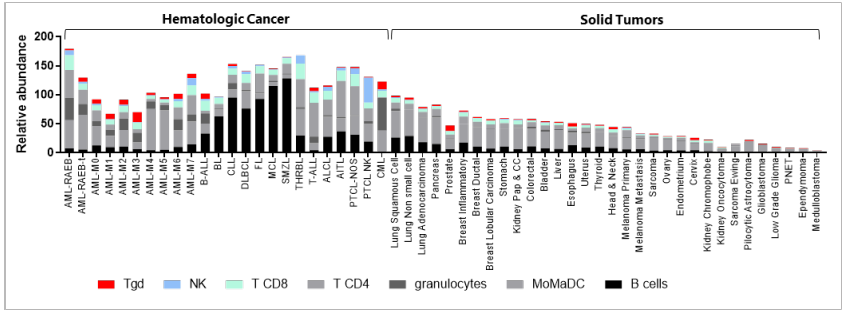
Patent holder: Patent Issued (not licensed): “Humanized and Chimeric Monoclonal Antibodies to CD81”, Stanford Office of Technology Licensing, U.S. Application Serial No. 62/351,054

Pre-Clinical and Clinical Research Grants (Institutional Funding): Merus, BMS, Boehringer Ingelheim, Transgene, Fondation MSD Avenir, Sanofi.

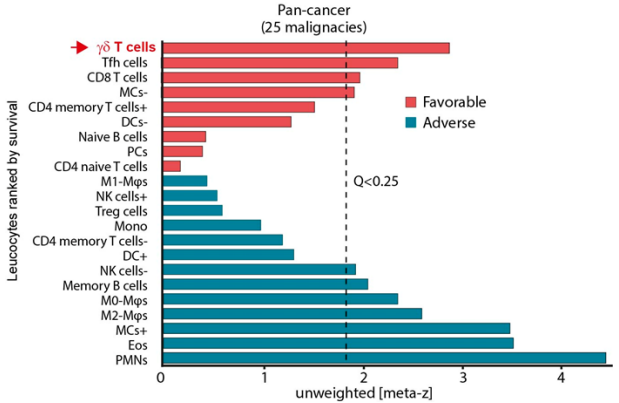
Editorial activities: Associate Editor at the *European Journal of Cancer*

Rationale for Activating γ9δ2 T Cells via Butyrophilin 3A

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

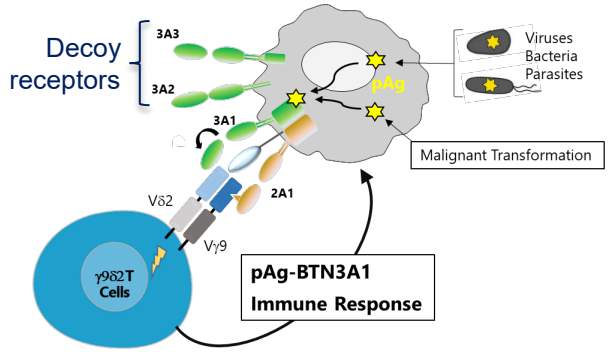


B. Strongest correlation with favorable prognosis of all TILs

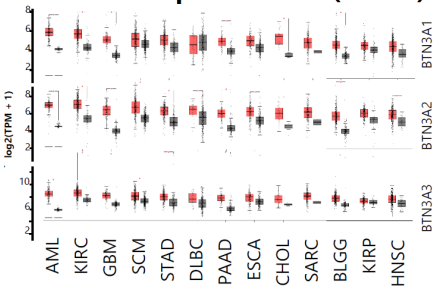


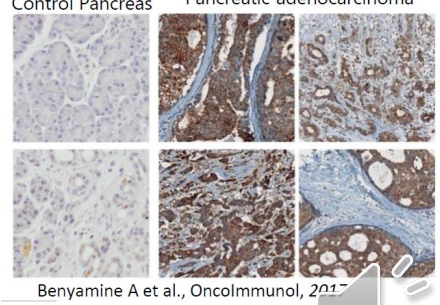
Adapted from Tosolini et al, OncoImmunol, 2017 and Gentles et al, Nat Med, 2015

C. Phosphoantigen (pAg)-BTN3A1-dependent stress signal selectively activates γ9δ2 T cells

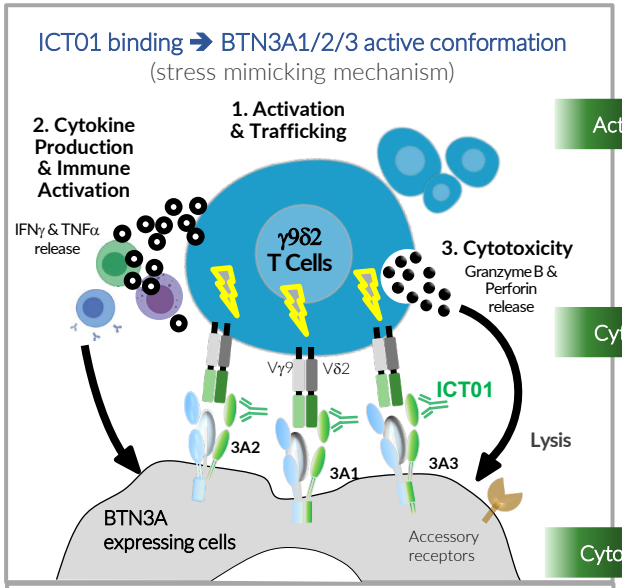


D. BTN3A Isoforms are overexpressed in multiple cancers



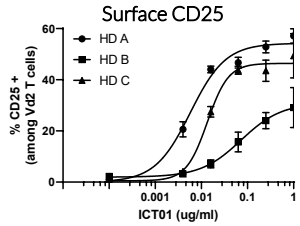


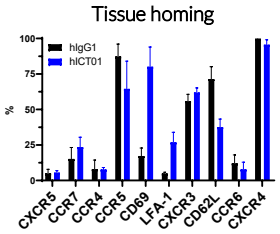
ICT01: a First-in-Class anti-BTN3A that Selectively Activates the Anti-Tumor Repertoire of γ9δ2 T Cells



1. Activation & trafficking in <30 min
2. Cytokines lead to recruitment of other immune cells, including NK cells, CD8 T cells and B cells
3. Cytotoxicity requires a 2nd confirmatory signal (e.g., NKG2D-MICA) to allow activated γ9δ2 T cells to kill stressed/malignant/infected cells

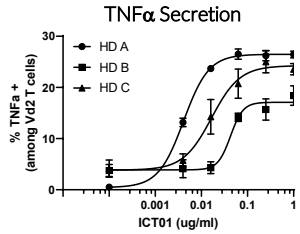
Activation

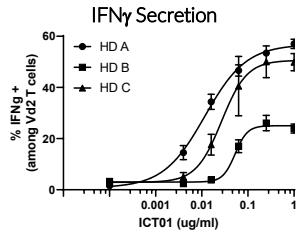




Migration into tumors

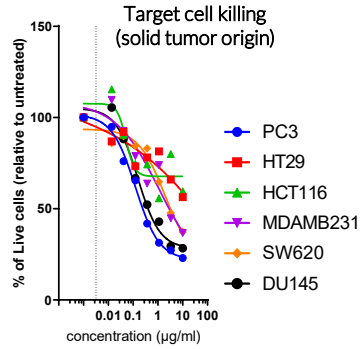
Cytokines

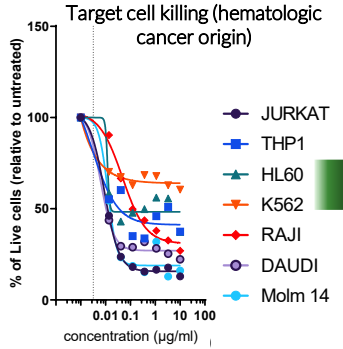




Expanded immune response & remodeling of TME

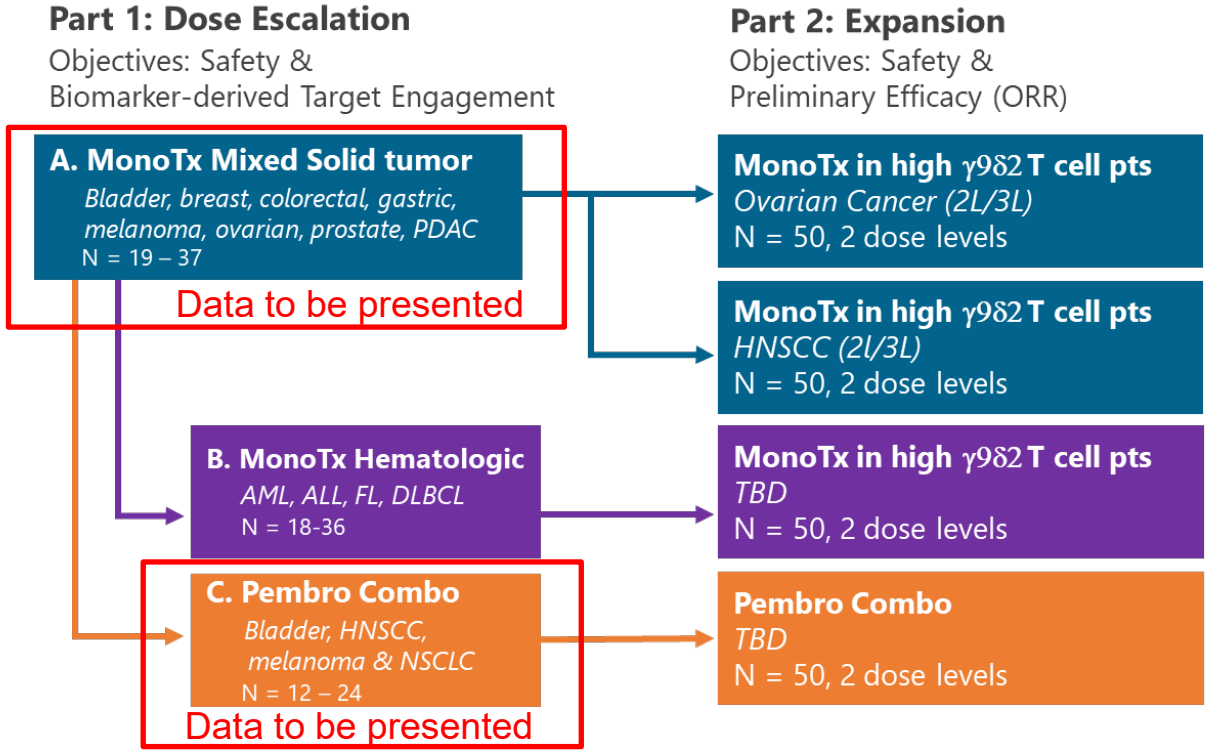
Cytotoxicity





Selective killing of malignant cells

EVICTION Trial Design: ICT01 as Monotherapy and in Combination with Pembrolizumab in Patients with Advanced, R/R Cancer



Part 1 Basket Indications:

1. BTN3A-expressing tumors
2. γδ T cell-infiltrating tumors

Part 1 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 biopsies
6. Pembro combo: failed ≥1 CPI & eligible per approved label

Participating Countries:

France, Belgium, Germany, Spain, UK and US

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Group A: Good Preliminary Safety & Tolerability of ICT01 in Solid Tumor Patients

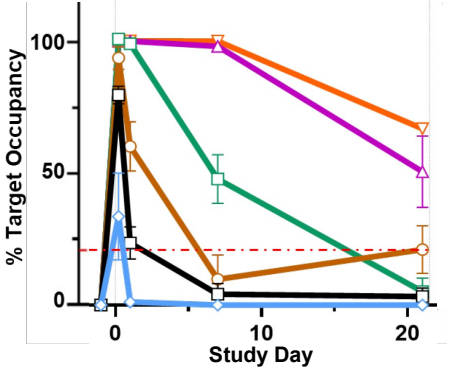
Cohort ICT01 Dose	Diagnosis	Age Range Sex	Mean # Prior CA Regimens (Range)	Possibly/Related AEs (n=1 unless specified)
Group A: ICT01 Monotherapy in Solid Tumors (n=32)				
Cohort 1 20-700 mcg	CRC x 3, Melanoma, Ovarian, PDAC	41-67 yo 4M/2F	5.6 (2-8)	Fever (2), Rash, Arthralgia, N/V
Cohort 2 2 mg	CRC 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
Cohort 5 75 mg	Breast x 2, CRC x 2, Gastric, Ovarian	28-70 yo 3M/3F	4.2 (2-6)	Fever (5), Chills (3), Rash, Conjunctivitis
Cohort 6 200 mg	CRC x 2, Gastric, Prostate x 3	45-79yo 6M	3.5 (1-6)	Fever (3), Chills, Shivering, N/V, Arthralgias, TIA (SAE), Allergic reaction (SAE)

Safety Summary:

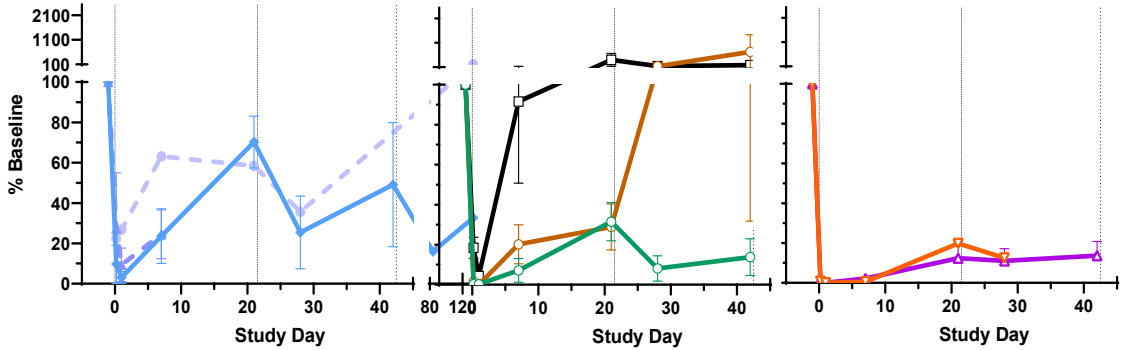
1. 1st dose fever/chills are most common AEs (all Grade 1/2; does not recur with subsequent doses)
2. Does not correlate with cytokines measured (IFNγ, TNFα, IL-6, IL-8), but may be cytokine-related
3. No DLTs or safety concerns/signals identified for ICT01

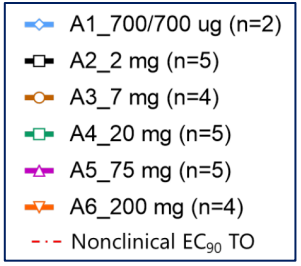
Group A: Pharmacodynamic Effects of ICT01

1. Dose-Dependent Binding of ICT01 to BTN3A on T Cells

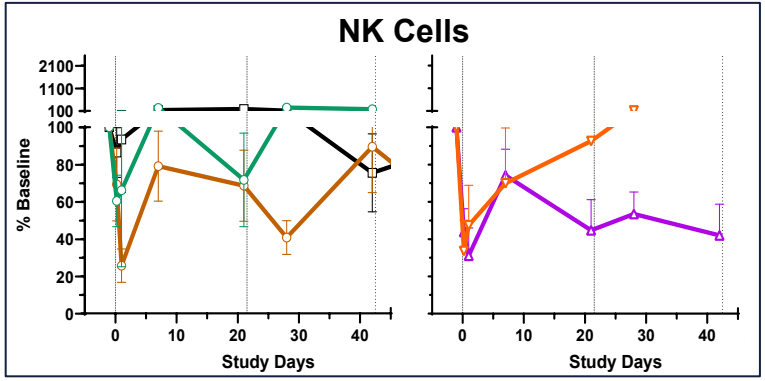


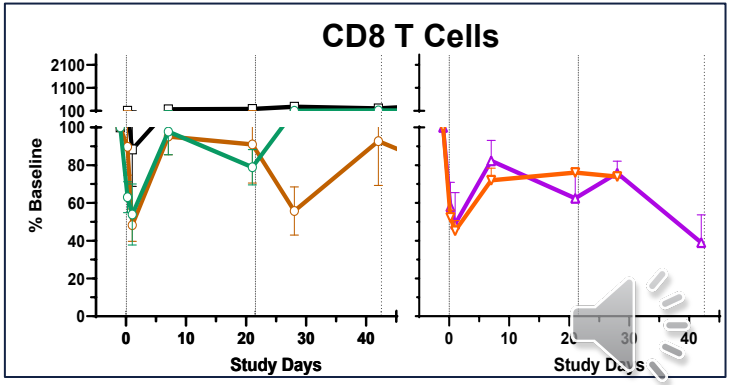
2. ICT01 Induces Dose-Dependent Migration of γ9δ2 T Cells from the Circulation





3. ICT01 Doses ≥ 7 mg Induce Migration of NK and CD8 T Cells





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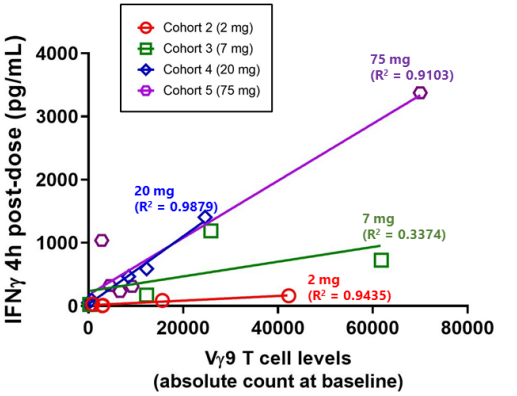
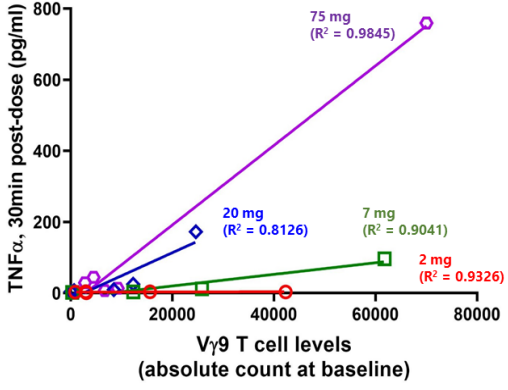
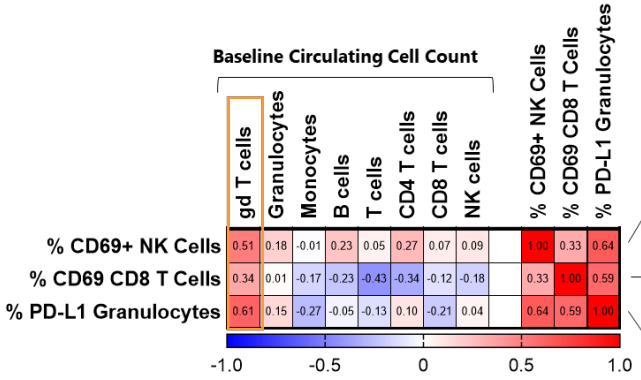
Increased IFNγ and TNFα Levels & Immune System Activation post ICT01: Correlation with Baseline γ9δ2 T Cells

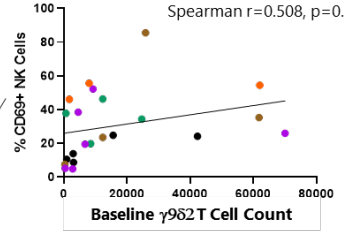
A. Peak Cytokine Levels post 1st Dose

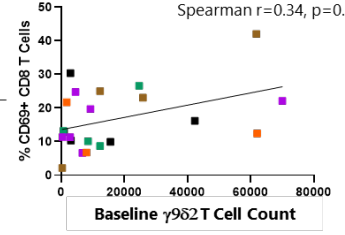


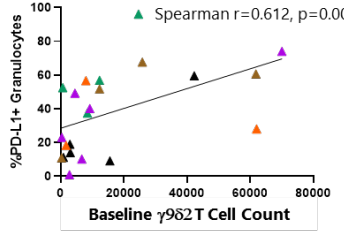


B. Activation of NK Cells, CD8 T Cells, and Granulocytes post-ICT01





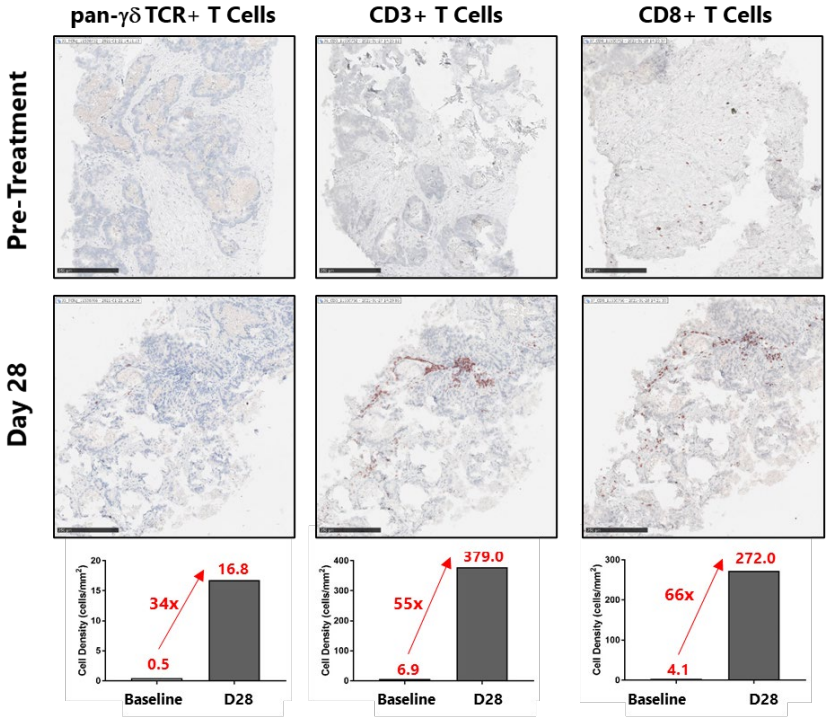




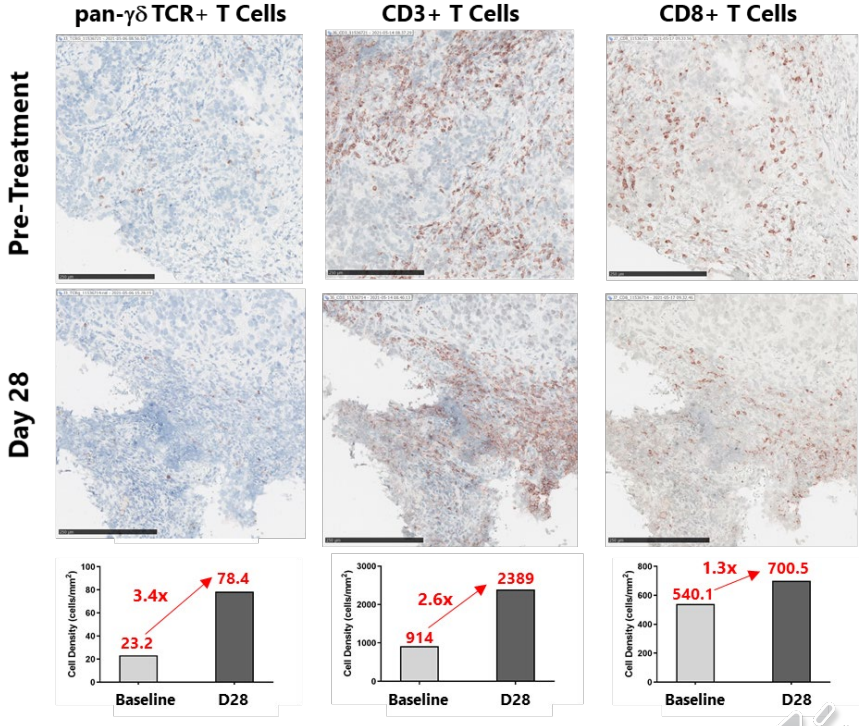
ICT01 Dose
- 2 mg
- 7 mg
- 20 mg
- 75 mg
- 200 mg

ICT01 Increases Tumor Infiltration of γδ, CD3 and CD8 T Cells

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

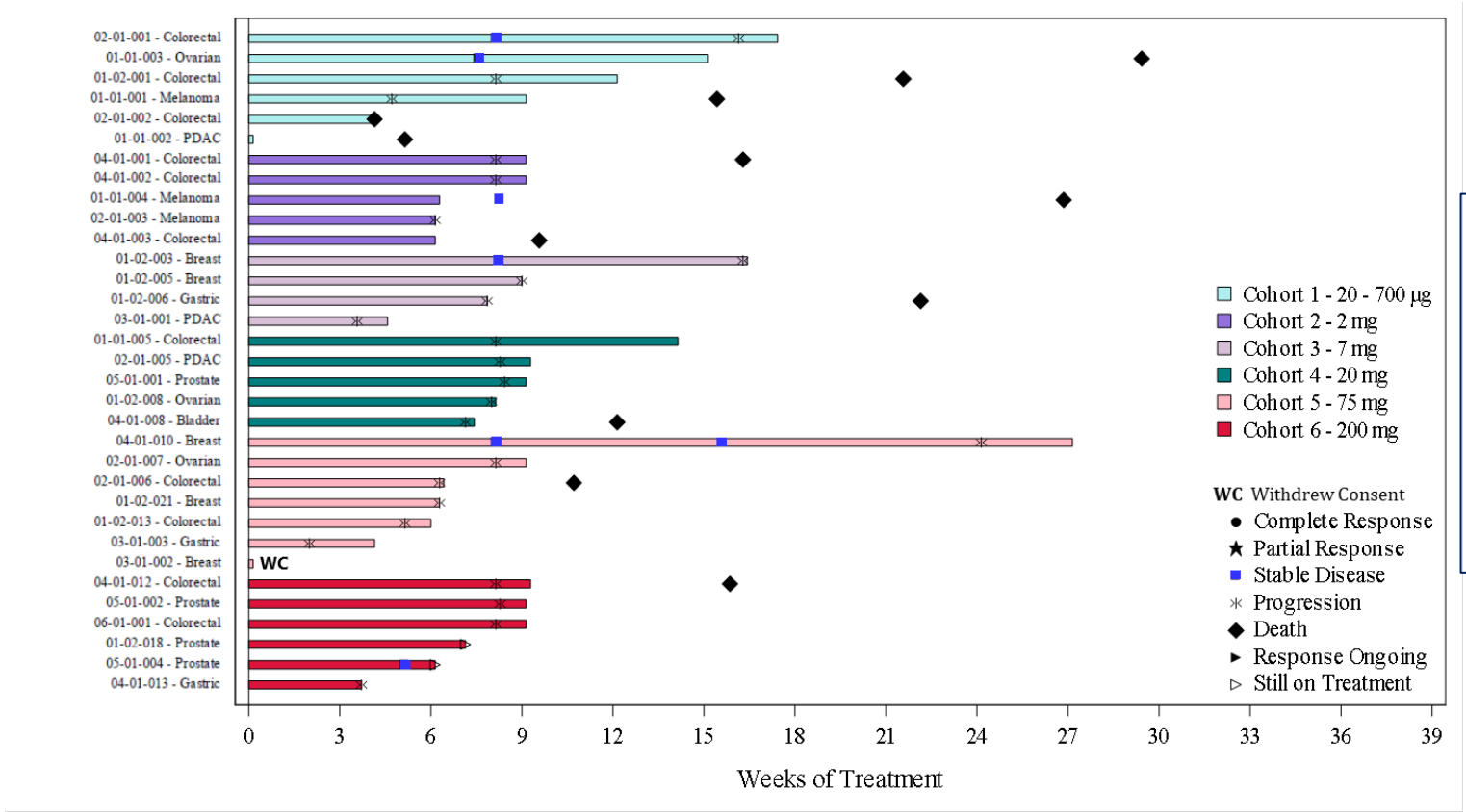


50-yo female with Ovarian Cancer (75 mg ICT01)



Digital Pathology: automated cell counts per mm² of tumor (HalioDx)

Group A Swimmer Plot: RECIST Performed Every 8 Weeks



ITT Efficacy:

Best response was SD in 6 of 33 patients

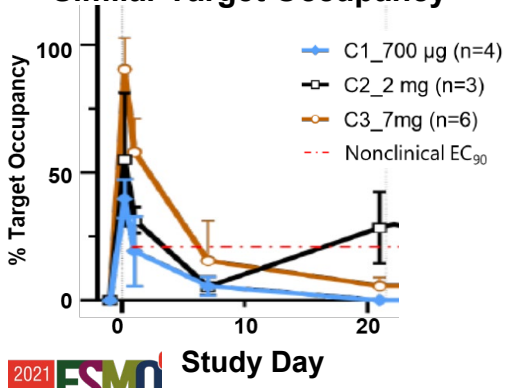
- 2 Breast
- 1 CRC
- 1 Ovarian
- 1 Melanoma
- 1 Prostate

Group C ICT01 + Pembro (200 mg IV Q3W): Similar Safety, Tolerability and PD Effects

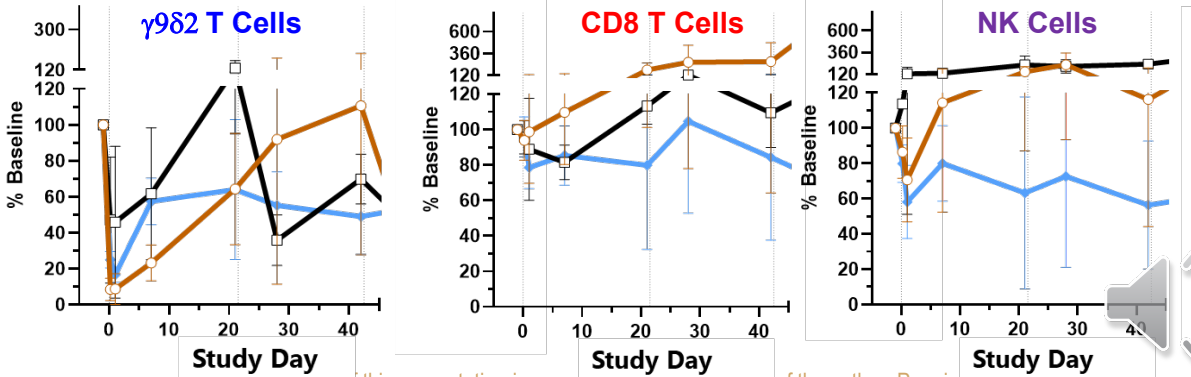
Cohort ICT01 Dose	Cancer Diagnosis (n)	Age Range Sex	Mean # Prior CA Regimens (Range) Prior CPI Treatment (n)	Possibly/Related AEs (n=1 unless specified)
Cohort 1 700 mcg	NSCLC, Bladder (2)	48-57 yo 1M/2F	3.7 (3-4) Avelumab (1), Nivo (1), Pembro (1), Investigational (1)	Rash, Fever, Dyspnea, Liver enzyme inc.
Cohort 2 2 mg	Bladder, Melanoma, NSCLC	60-72 yo 1M/2F	2.7 (2-4) Nivo (1), Ipi/Nivo (1), Pembro (1)	Fever, CRS (G1, fever), shoulder pain, asthenia, diarrhea
Cohort 3 7 mg	Bladder (3), NSCLC (2) Melanoma	61-84yo 4M/2F	2.8 (2-4) Nivo (2), Pembro (3), Investigational (1)	Asthenia (2), IRR (G2, Shivers)

Safety Summary: No DLTs or new safety signals. ICT01 20 mg dose cohort enrolling.

1. ICT01 + Pembro Produces Similar Target Occupancy



2. Low Dose ICT01 + Pembro Induces Similar Migration of Circulating γ9δ2 T Cells and Variable Effects on CD8 T Cells and NK Cells



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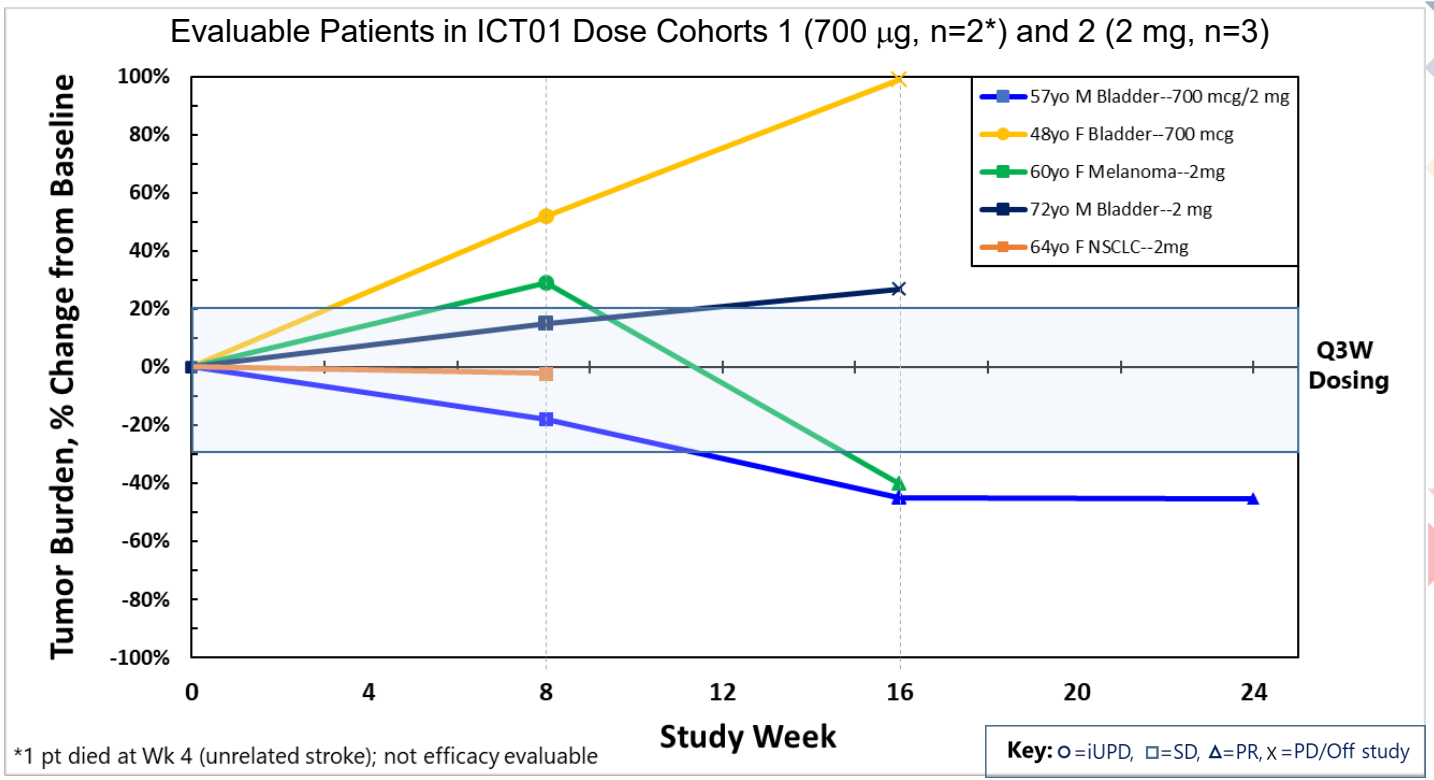
Group C ICT01 + Pembro 200mg IV: Spider Plot



Patients in Dose Cohort 3 (7 mg ICT01+Pembro) have not reached first efficacy evaluation at Week 8.

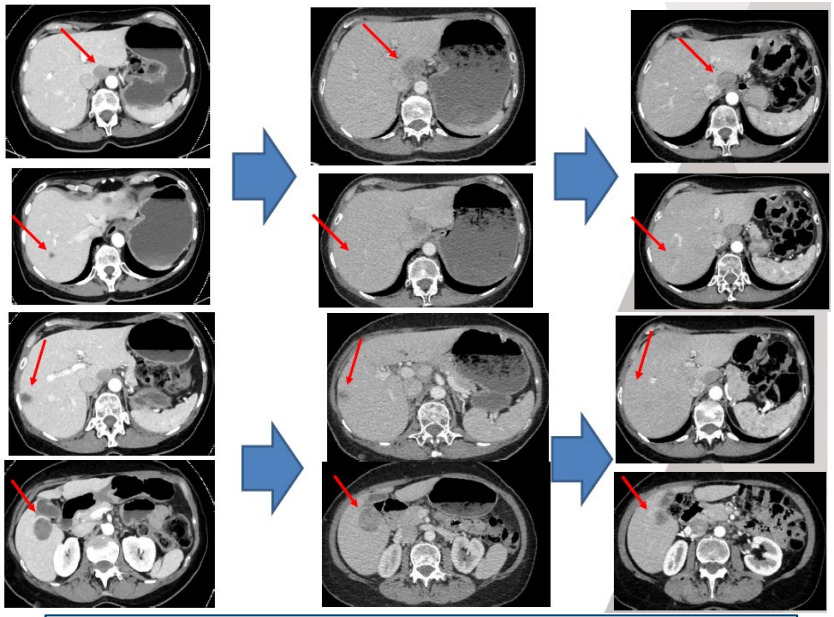
Aurélien Marabelle, MD, PhD

60yo Female with Metastatic Melanoma: CNS & Liver Mets (Ipi/Nivo Refractory)

7 APR 2021
Baseline

11 JUN 2021
C3D14: iuPD (+29%)

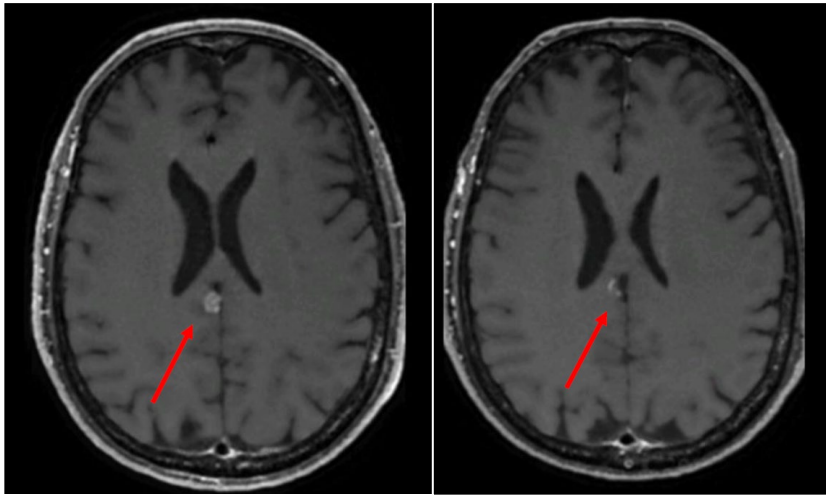
7 JUL 2021
C4D21: iSD (-9%)



Scans on 17 AUG 2021 (C6D20) showed
-40% in tumor burden (RECIST)

14 APR 2021
C1D1 (pre-dose)

26 MAY2021
C3D1 (pre-dose)



8 mm lesion

4 mm lesion

Aurélien Marabelle, MD, PhD

Summary of Solid Tumor Experience in EVICTION

ICT01 Monotherapy

1. Dose escalation completed in monotherapy without any observed DLTs and strong PD effects on cytokines and tumor-infiltrating CD8 T cells that are linked to baseline $\gamma 9\delta 2$ T cell counts.
2. Part 2: Cohort Expansion of ICT01 monotherapy in ovarian and HNSCC patients with high baseline $\gamma 9\delta 2$ T cells ($\geq$ 20K/mL blood) planned to start Q4 2021.

ICT01 Combination with Pembrolizumab

1. Dose escalation ongoing with no DLTs observed up to 7 mg ICT01 + 200 mg Pembro.
2. Preliminary signs of tumor regression observed at low ICT01 doses may reflect the contribution of remodeling of the tumor immune microenvironment by ICT01 that increases tumor infiltration of CD8 T cells, which can be activated by an anti-PD-1 agent like pembrolizumab.
3. Additional experience with the combination needed to confirm these results.

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- ***Profound thanks to the patients that participated in the study.***
- *Special thanks to the site investigators and the clinical study teams at Gustave Roussy, Jules Bordet, Institut Paoli Calmettes, Institute for Cancer Research, Vall d'Hebron Institute of Oncology, NCT/UCC-ECTU Dresden and Yale Cancer Center.*
- *Acknowledgement of our research partners at iLifeConsulting, Precision for Medicine, and HalioDx.*

European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org
esmo.org