Abstract #9534

EVICTION study: ICT01, an anti-Butyrophilin 3A monoclonal antibody activating γ9δ2 T cells in combination with pembrolizumab in checkpoint inhibitor refractory melanoma

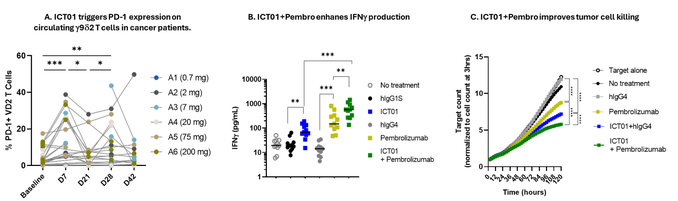
Stéphane Champiat[1], Martin Wermke[2], Cecile Vicier[3], Johann De Bono[4], Emiliano Calvo[5], Jorge, Ramón[5], Evan Hall[6], Elena Garralda[7], Vladimir Galvao[7], Emanuela Romano[8], Antoine Italiano[9], Esma Saada,[10] Benoit You[11] , Aude De Gassart[12], Emmanuel Valentin[12], Marina Iché[13], Maelle Mairesse[12], Patrick Brune[12], Katrien Lemmens[12], Daniel Olive[14], Paul Frohna[12]

[1]Gustave Roussy, Paris, France; [2]Medical Faculty Carl Gustav Carus, Technical University, Dresden, Germany; [3]Institut Paoli Calmettes, Marseille, France; [4]The Institute for Cancer Research and Royal Marsden, London, UK; [5]START Madrid, CIOCC, Madrid, Spain; [6]University of Washington, Fred Hutchinson Cancer Center, Seattle, WA; [7]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [8]Center for Cancer Immunotherapy, Institut Curie, Paris, France; [9]Institut Bergonié, Bordeaux, France; [10]Centre Antoine Lacassagne, Nice, France; [11]Lyon Sud Hospital, Oullins-Pierre-Bénite, France; [12]ImCheck Therapeutics, Marseille, France; [13]Ilife Consulting, Paris, France; [14]Centre de recherche en Cancérologie de Marseille, INSERM U1068, CNRS U7258, Aix Marseille Université, Institut Paoli-Calmettes, Marseille, France.

INTRODUCTION

- ICT01, an anti-BTN3A mAb, selectively activates γ9δ2 T cells.
- γ9δ2 T cell tumor infiltration is associated with a favorable prognosis making stimulation of these cells a new potential target for anti-tumor immunotherapy.
- ICT01-modulated activation of γ9δ2 T cells increases surface expression of PD-1 in vitro and in blood of cancer patients treated in Group A of EVICTION (Figure 1A) and combination with pembrolizumab (PEM) leads to enhanced IFNγ production and cancer cell killing (Figure 1B & C).

Figure 1: ICT01 Increases PD-1 expression and potentiates pembrolizumab anti-tumor activity



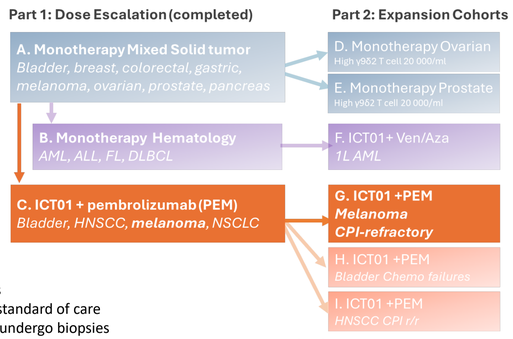
PD-1 expression on PBMC of cancer patients treated with escalating doses of ICT01 (EVICTION Group A) at basline and at day (D)7, D21 (prior 2nd dosing), D28 and D42 (prior 3rd dosing). *** p<0.001, ** p<0.01; * p<0.05

IFNγ (ELISA) in supernatant of human isolated T cells co-cultured with allogenic MoDC in presence of indicated antibodies. *** p<0.001, ** p<0.01.

Growth over time of BTN3A and PD-L1 expressing SK-OV-3 cells co-cultured with HD-PBMC (n=8) in presence of ICT01 (0.1 µg/mL), Pembrolizumab (10 µg/mL) or the combination. Incucyte live imaging monitoring. **** p<0.0001.

STUDY DESIGN EVICTION AND METHODS

Figure 2: EVICTION Phase 1/2a study design



Eligibility:
- M/F > 18 years
- No remaining standard of care
- Willingness to undergo biopsies
- Group C: disease progression, failed ≥ 1 checkpoint inhibitor (CPI)
- Group G: CPI-refractory melanoma, primary resistance per SITC 2020 (no prior PR or SD for 6 months)

Treatment:
- Part 1: dose escalation of ICT01 20 µg to 200 mg IV, Q3W + PEM 200 mg IV Q3W
- Part 2: randomization to ICT01 7 mg or 200 mg IV Q3W + PEM 200 mg IV Q3W

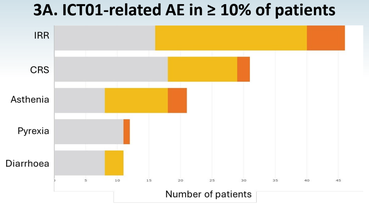
Efficacy assessment by RECIST 1.1 Q8W:
- Intention to treat population (ITT) = all enrolled; efficacy evaluable population (EE) = received 3 doses and scan
- Disease Control Rate (DCR)= Complete Response (CR) + Partial Response (PR) + Stable Disease (SD ≥6 months)
- Objective Response Rate (ORR) = CR + PR; no response (NR) = best response disease progression

Biomarkers:
- Flow cytometry on fresh blood samples for receptor occupancy (20.1 mAb) and BTN3A membrane expression (non-competing 103.2 mAb)
- Proinflammatory Panel 1 by Mesoscale Discovery (MSD) platform for multiplexed cytokine analyses
- Baseline and on-treatment (day 28) biopsies, formalin-fixed, paraffin-embedded (FFPE)

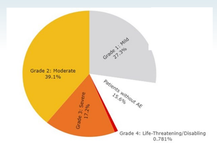
ICT01 + PEM SAFETY PROFILE

Figure 3: ICT01-related adverse events (AE) in solid tumor patients of EVICTION treated with ICT01 + PEM (n=130) demonstrate a manageable safety profile

3A. ICT01-related AE in ≥ 10% of patients



3B. Treatment-related AE per severity



- Infusion related reaction (IRR, in 36 %) and cytokine release syndrome (CRS, in 24%) are mostly Grade 1/2 presenting as fever and chills. In some cases, mild hypotension occurs requiring no vasopressor treatment. Tocilizumab was administered in 2 cases for Grade 2 CRS.
- Most common Grade 3 ICT01-related AEs are IRR and CRS in 6 (8%) and 4 (3%) patients, respectively and recovered within 48 hours upon treatment including corticosteroids (n=8) and/or adrenaline (n=2).

CPI-REFRACTORY MELANOMA COHORT

Figure 4: CPI-refractory melanoma patients enrolled in EVICTION

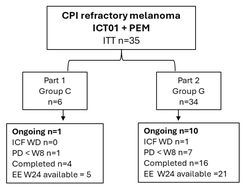


Table 1: Prior lines of therapy

Prior Lines of treatment	n	%
1 prior line	6	15%
≥2 prior lines	34	85%
Prior Metastatic CPI		
1 prior CPI	25	62%
≥2 prior CPI	7	18%
Prior anti- BRAF/MEK	11	28%

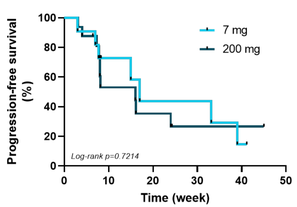
85% of patients are 2+L

CLINICAL EFFICACY IN 2+L CPI-REFRACTORY MELANOMA

Table 2: DCR in CPI-refractory melanoma

CPI refractory melanoma	n	ITT N=35	EE N=26
Total DCR	8	23%	31%
PR	3	9 %	12%
SD ≥ 6 months	5	14%	19%

Interim efficacy data:
- **DCR of 31 %**
- **ORR of 12 %**
- **median duration of PR response of 14.7 months**



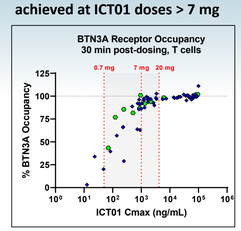
	n	# of Events	Median PFS (95% CI)
7 mg	13	7	**17 weeks** (0.40 – 2.79)
200 mg	18	10	**16 weeks** (0.36 – 2.47)

Figure 5: Progression Free Survival (PFS) in CPI-refractory melanoma demonstrates a median PFS ≈3.9 months

BIOMARKER DATA

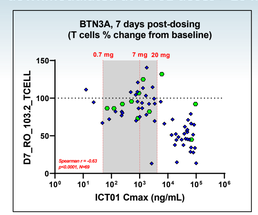
Figure 6: BTN3A receptor occupancy and membrane expression on circulating T cells

6A. Full BTN3A receptor occupancy achieved at ICT01 doses > 7 mg



ICT01 receptor (BTN3A) occupancy on 30 min post-dose fresh blood samples in relation to ICT01 peak levels (Cmax) .

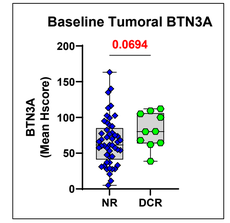
6B. BNT3A membrane expression is downmodulated at ICT01 doses > 20 mg



BTN3A membrane expression on circulating T cells pre-dose and on day (D) 7 in relation to ICT01 peak levels (Cmax). MFI values shown are percent changes from pre-dose. Spearman correlation.

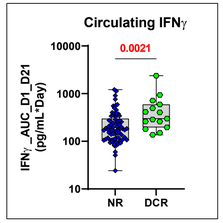
Figure 7: DCR is associated with BTN3A tumoral expression (A), elevation of circulating IFNγ (B), and increased tumoral CD8 T cell proliferation (C) and PD-L1 expression (D)

7A



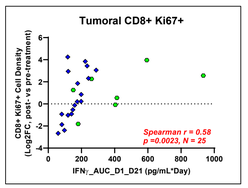
BTN3A in baseline tumoral biopsies presented as mean all Histo (H)-Scores of 3 different IHC methods, cytoplasmic and membranous signals. Mann-Whitney t-test.

7B

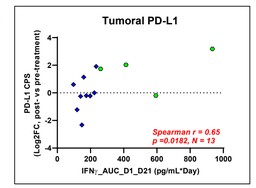


Area under the curve (AUC, pg/mL*day) of circulating IFNγ levels on day (D) 1, D7, D14 and D21. Mann-Whitney t-test.

7C



7D



Area under the curve (AUC, pg/mL*day) of circulating IFNγ levels, on day (D) 1, D7, D14 and D21. Multiplex IHC staining on tumoral biopsies (FFPE, digital pathology, number of CD3+/CD8+/Ki67+ triple positive cells per mm², PD-L1 scoring (CPS), Log2FC post vs pre-treatment). Spearman correlation.

CONCLUSIONS

- ICT01 in combination with PEM has a manageable safety profile.
- ICT01 in combination with PEM demonstrates efficacy data in 2+L CPI refractory melanoma patients warranting further investigation.
- DCR is related to baseline tumoral BTN3A expression, sustained elevation of IFNγ levels, and expression of markers of tumor microenvironment remodeling.
- Patient selection based on BTN3A tumor expression will be further evaluated as a potential enrichment strategy.