ICT01, a γ9δ2 T-Cell-activating mAb, in combination with pembrolizumab elicits deep and durable responses in second-line patients with primary refractory melanoma: **results from EVICTION study**

Abstract #1307

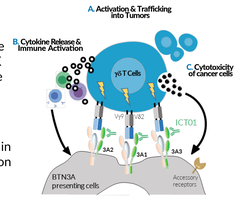
Stephane Champiat, Johann de Bono, Cecile Vicier, Emiliano Calvo, Evan Hall, Elena Garralda, Antoine Italiano, Benoit You, Hatem Soliman, Tatiana Hernandez, Christiane Jungels, Esma Saada, Julien Vibert1 , Aude De Gassart, Emmanuel Valentin, Clement Ghigo, George Saad, Maelle Mairesse, Patrick Brune, Katrien Lemmens, Daniel Olive, Stephan Braun, Martin Wermke

S.C. Gustave Roussy, Paris (FRA) | ***J.DB.*** The Institute for Cancer Research and Royal Marsden, London (UK) | ***C.V.*** Institut Paoli Calmettes, Marseille (FRA) | ***E.C.*** START Madrid CIOCC, Centro Integral Oncológico Clara Campal, Madrid (SPAIN) | ***E.H.*** University of Washington, Fred Hutchinson Cancer Center, Seattle, WA (USA) | ***E.G.*** Vall d'Hebron Institute of Oncology (VHIO), Barcelona (SPAIN) | ***A.I.*** Institut Bergonié, Bordeaux (FRA) | ***B.Y.*** CITOHL, EPSILYON, Hospices Civils de Lyon, IC-HCL, CICLY (FRA) | ***H.S.*** Clinical Trials Office and Phase 1 program, Moffitt Cancer Center, FL (USA) | ***T.H.*** START Barcelona-HM CIOCC, Hospital HM Nou Delfos, Barcelona (SPAIN) | ***C.J.*** Institut Jules Bordet, Brussels (BELGIUM) | ***E.S.*** Centre Antoine Lacassagne, Nice (FRA) | ***A.DG., E.V., C.G, G.S, M.M., P.B., K.L., S.B.*** ImCheck Therapeutics, Marseille (FRA) | ***D.O.*** Centre de Recherche en Cancérologie de Marseille, Aix Marseille Université, Institut Paoli-Calmettes, Marseille (FRA) | ***M.W.*** Medical Faculty Carl Gustav Carus, Technical University, NCT/UCC Early Clinical Trial Unit, Dresden (GERMANY).

INTRODUCTION

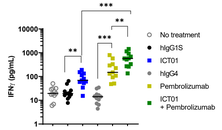
- ICT01 is a first-in-class humanized, Fc-disabled anti-butyrophilin 3A (BTN3A) monoclonal antibody that selectively activates γ9δ2 T cells (Figure 1).
- ICT01 leads to direct cytotoxicity against tumor cells and indirect cytotoxic immune effects through remodeling of the tumor microenvironment by activated γ9δ2 T, CD8, and NK cells, which is postulated to overcome resistance to immune checkpoint inhibitors and chemotherapy.
- *In vitro*, ICT01 combination with pembrolizumab leads to enhanced IFNγ production and cancer cell killing (Figure 2).
- In study EVICTION (NCT04243499), ICT01-pembolizumab in combination is being investigated in patients that progress on one prior line of checkpoint inhibitor (CPI) therapy.

Figure 1: ICT01 mode of action

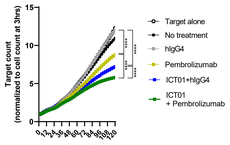


De Gassart et al, Science Translational Medicine, 2021

Figure 2: ICT01 potentiates pembrolizumab anti-tumor activity



IFNγ in supernatant of human isolated T cells co-cultured with allogenic monocyte-derived dendritic cells in the 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 healthy-donor-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.

SAFETY OF ICT01 + PEMBROLIZUMAB

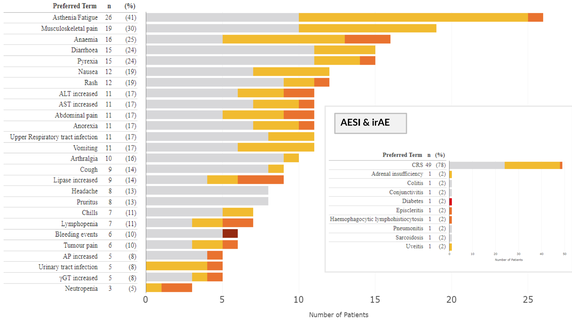
Table 1: Safety summary for melanoma patients treated with ICT01+pembrolizumab in EVICTION

TEAE category [n (%)]	ICT01+pembrolizumab		
	Group C (N=12)	*Group G* (N=51)	Pooled (N=63)
Patients with any AE	**12 (100)**	**51(100)**	**63 (100)**
Maximum CTCAE Grade 1	1 (8)	4 (8)	5 (8)
Maximum CTCAE Grade 2	5 (42)	25 (49)	30 (48)
Maximum CTCAE Grade 3	5 (42)	18 (35)	23 (37)
Maximum CTCAE Grade 4	1 (8)	2 (4)	3 (5)
Maximum CTCAE Grade 5	0	2 (4)	2 (3)
Patients with any drug-related* AE	**12 (100)**	**48 (94)**	**60 (95)**
Maximum CTCAE Grade ≥ 3	3 (25)	10 (20)	13 (21)
Patients with any SAE	**3 (25)**	**19 (37)**	**22 (35)**
Patients with any drug-related* SAE	2 (17)	9 (18)	11 (17)
Patients with any AE leading to permanent study discontinuation	**0**	**1 (2)**	**1 (2)**
Patients with any drug-related AE leading to permanent study discontinuation	0	1 (2)	1 (2)
Patients with any AE leading to treatment interruption and/or dose reduction	**3 (25)**	**9 (18)**	**12 (19)**
Patients with drug-related AE leading to treatment interruption and/or dose reduction	3 (25)	7 (14)	10 (16)
Patients with any AE leading to death	**0**	**2 (4)**	**2 (3)**
Patients with any drug-related AE leading to death	0	0	0

Reasons for treatment discontinuation: pneumonitis (n=1), *possibly/probably related* to ICT01;
Reasons for treatment interruption: CRS (n=5), laboratory abnormalities (n=2), immune-related AE (n=2), other (n=1), all *possibly/probably related* to ICT01 and/or pembrolizumab —laboratory abnormalities (n=1), other (n=1), all *unlikely related* to ICT01.
Reasons for death: myocardiitis and tumor haemorrhage, each n=1, all deaths *unlikely related* to ICT01.

The category 'any TEAE' comprises all emerging adverse events, including unlikely/possible/probably related events.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious AE; TEAE, treatment-emergent AE.

Figure 3: Treatment-emergent adverse events occurring in ≥ 10% of melanoma patients or Grade ≥ 3 (Group C and G, N=63)



CTCAE categories: Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5.

Abbreviations: AESI, adverse event of special interest; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; irAE, immune-related adverse event; PEM, pembrolizumab.

CRS as most frequent on-target adverse events is mostly mild (no Grade 4 and 5) and in 84% of the cases occurs after the first dose only.

EFFICACY OF ICT01 + PEMBROLIZUMAB IN 2L MELANOMA

Figure 5: Anti-tumor efficacy of ICT01+pembrolizumab in 2L CPI-refractory or CPI-relapsed metastatic melanoma patients (N=27)

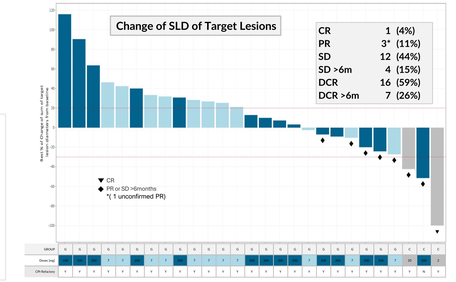
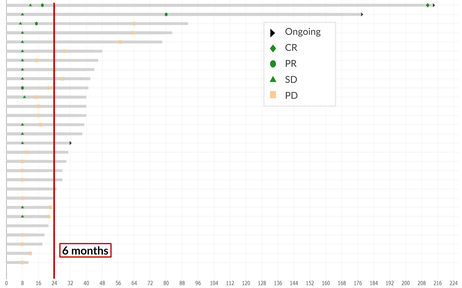


Figure 6: Treatment and response duration to ICT01+pembrolizumab in 2L CPI-refractory or CPI-relapsed metastatic melanoma patients (N=27)



Abbreviations: 2L, second-line treatment; 6m, 6 months; CPI, (immune) checkpoint inhibitor; DCR, disease control rate; Group C, ICT01+pembrolizumab dose-escalation cohorts; PR, partial response, SD, stable disease; SLD, sum of largest diameter; NC, non-cutaneous; UNK, Unknown.

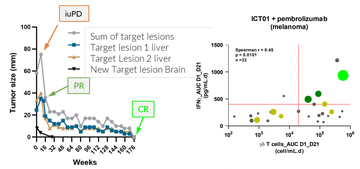
Table 3: Efficacy signal with ICT01+pembrolizumab compares favorably with benchmark studies

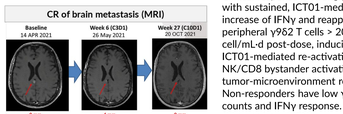
Variables	ICT01+pembro 2L R/R melanoma* (N=27)	Ipi+nivo[1] SWOG S1616 CPI-refractory (no 1L CR or PR) (N=69)	OPDUALAG[2] R/R[!] 2L+ (N=351)	Pembro+ipi[4] R/R[!] 2L+ (N=70)
EFFICACY				
ORR [%] (CI)	**15*** (4–34)	**28** (19–38)	**12** (7–18)	**27** (18–41)
mPFS [months]	**3.5** (95%CI, 1.9–5.5)	–	2 (95% CI 2–4)	5 (95% CI, 3–8)
PFS 6 months [%] (CI)	**26** (14–49)	**34** (25–43)	**29** (24–34)	–
DoR, median [months] (CI)	**9.5** (95%CI, 2–NR)	**41** (90% CI, 8–NR)	NR (12.9–NR)	**16** (95% CI, 8–NR)
SAFETY				
Grade ≥ 3 TRAE (%)	**26**	**50**	**15**	**27**
AEs leading to discontinuation [n]	-	**29**	**5**	–

* 1 unconfirmed PR

References: **1** Olsen et al. J Clin Oncol 2021;39:2647-2655. | **2** Ascierto et al. J Clin Oncol 2023;41:2724-2735. | **3** VanderWalde et al. Nat Med 2023;29:2278–2285.

Figure 7: Complete Response with 2 mg ICT01–pembrolizumab in 2L CPI-refractory melanoma patient showcasing mode of action of ICT01



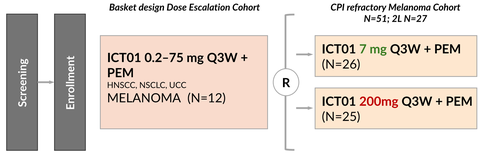


Clinical response is strongly associated with sustained, ICT01-mediated increase of IFNγ and reappearance of peripheral γ9δ2 T cells > 20,000 cell/mL·d post-dose, inducing cyclic ICT01-mediated re-activation triggering NK/CD8 bystander activation and tumor-microenvironment remodeling. Non-responders have low γ9δ2 T-cell counts and IFNγ response. Patient with CR had highest IFNγ response and γ9δ2 T-cell counts.

STUDY DESIGN AND METHODS

Key eligibility criteria of melanoma patients:

- Group C: failed ≥ 1 checkpoint inhibitor (CPI)
- Group G: CPI-refractory melanoma, primary resistance per SITC 2020 criteria (no prior PR or SD for 6 months); 2L subgroup (n=22) failed one prior line of CPI



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:

- Disease Control Rate (DCR)= Complete Response (CR) + Partial Response (PR) + Stable Disease (SD)
- Objective Response Rate (ORR) = CR + PR

Biomarkers:

- BTN3A receptor occupancy (20.1 mAb) and BTN3A membrane expression (non-competing 103.2 mAb)
- Multiplexed cytokine analyses (MSD platform, Proinflammatory Panel 1)
- Baseline and on-treatment (D28) biopsies

References: Kluger HM et al. J Immunother Cancer 2020

Abbreviations: CPI, checkpoint inhibitor; DCR, disease control rate, comprising complete response + partial remission + stable disease; ICT01, anti-BTN3A (also known as CD277) monoclonal antibody (given Q3W in combination with PEM); IV, intravenously; Q3W, every three weeks; PEM, pembrolizumab (given Q3W); R, randomization;

PATIENT CHARACTERISTICS

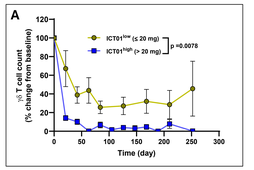
Table 2: Patient characteristics of 2L melanoma patients treated with ICT01+pembrolizumab

Variables [n (%)] or [median (range)]	ICT01+pembrolizumab		
	2L Melanoma N=27	CR N=1	PR N=3
Age, years	57 (29–77)	60	68 (53-68)
< 65 years	18 (67)	1	1
Subtypes of melanoma			
Cutaneous	16 (59)		
Mucosal	5 (19)	1	1
Other/Unknown	6 (22)		2
Baseline LDH			
< 2 x ULN	21 (78)		2
≥ 2 x ULN*	6 (22)	1	1
Presence of liver metastases			
Yes	12 (44)	1	1
No	15 (56)		2
Prior (neo)adjuvant immunotherapy	11 (41)		1
Prior BRAF/MEK	7 (26)	1	
Prior metastatic immunotherapy	19 (70)	1	1

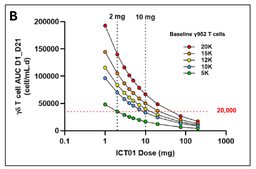
*Includes patients with missing data.

DOSE SELECTION

Figure 4: Dose selection 10 mg ICT01 for combination with pembrolizumab



A) Continued dosing of ICT01 > 20 mg leads to sustained depletion of γ9δ2 T cells suggesting overactivation-induced cell death.



B) Modeling based on ICT01 Cmax and γ9δ2 T-cell baseline counts yields an optimal γ9δ2 T-cell AUC ≥ 20,000 cell/mL·d (associated with IFNγ⇧) achievable with 10 mg.

Abbreviations: AUC, area under the curve; IFNγ, interferon-gamma; NHP, non-human primates; Q3W, every 3 weeks.

SUMMARY AND CONCLUSION

- ICT01+pembrolizumab in doses up to 200 mg showed a manageable safety profile with asthenia, and cytokine release syndrome as most frequent AEs and overall rare serious and immune-related AEs; CRS is considered MoA-related on-target toxicity, usually low-grade and a first-cycle event in the majority of patients (84% of events).
- ICT01+pembrolizumab demonstrated clinically meaningful anti-tumor efficacy in 2L CPI-refractory metastatic melanoma patients indicating the potential to overcome resistance to checkpoint inhibitors and chemotherapy.
- Anti-tumor response is related to sustained elevation of IFNγ levels and cyclic reappearance of γ9δ2 T cells during the dosing interval, a prerequisite of cyclic ICT01-mediated re-activation, both resulting in NK/CD8 bystander activation of anti-tumor effects and contributing to tumor-microenvironment remodeling.
- The dose of 10 mg ICT01 Q3W is proposed for future clinical studies investigating the potential of ICT01-pembrolizumab.

Scan Me