ICT01 and pembrolizumab in combination elicit deep and durable responses in patients with second line refractory melanoma: **interim results from study EVICTION**

Abstract #692

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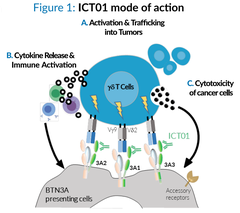
INTRODUCTION

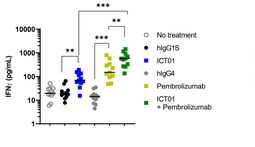
- ICT01 is a first-in-class humanized, Fc-disabled anti-butyrophilin 3A (BTN3A) monoclonal antibody that selectively activates γ9δ2 T cells (Figure 1).
- ICT01 leads to direct cytotoxicity against tumor cells and indirect cytotoxic immune effects through remodeling of the tumor microenvironment by activated 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-pembrolizumab in combination is being investigated in patients that progress on one prior line of checkpoint inhibitor (CPI) therapy.

Figure 1: **ICT01 mode of action**

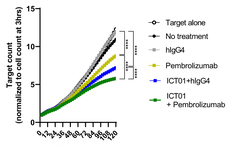


De Gassart et al, Science Translational Medicine, 2021

Figure 2: **ICT01 potentiates pembrolizumab anti-tumor activity**



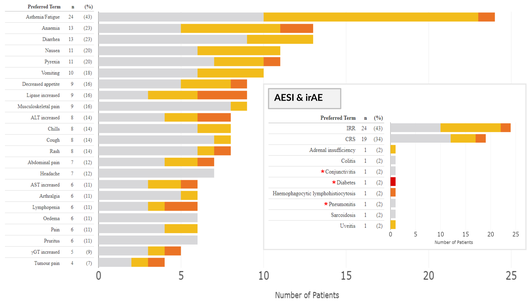
IFNγ in supernatant of human isolated T cells co-cultured with allogenic monocyte-derived dendritic cells in the presence of indicated antibodies *** p<0.001, ** p<0.01.



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

Figure 4: **AEs occurring in ≥ 10% of melanoma patients or Grade ≥ 3 (Group C and G, N=56)**



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

Abbreviations: AE, adverse event; AESI, adverse event of spcial interest; ASTCT, American Society for Transplantation and Cellular Therapy, CRS, cytokine release syndrome; CTCAE, common terminology criteria for adverse events; Group C, ICT01+pembrolizumab dose-escalation cohorts; irAE, immune-related adverse event; IRR, infusion-related reaction; PEM, pembrolizumab.

Most frequent adverse events were asthenia (43%), infusion related reaction (IRR, 43%) and cytokine release syndrome (CRS,34%). Serious TRAEs (Grade ≥ 3) and immune-related AEs (Grade ≥ 2) were overall rare. All CRS were managed with antipyretics and corticosteroids and recovered within 24-72h. No prophylactic treatment was given.

* occurred in same patient.

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

AE category [n (%)]	ICT01+pembrolizumab Group C (N=12)	Group G (N=44)	Pooled (N=56)
Patients with any AE	**12 (100)**	**44 (100)**	**56 (100)**
Maximum CTCAE Grade 1	1 (8)	4 (9)	5 (9)
Maximum CTCAE Grade 2	5 (42)	20 (45)	25 (45)
Maximum CTCAE Grade 3	5 (42)	17 (39)	22 (39)
Maximum CTCAE Grade 4	1 (8)	1 (2)	2 (4)
Maximum CTCAE Grade 5	0	2 (5)	2 (4)
Patients with any drug-related* AE	**12 (100)**	**41 (93)**	**53 (95)**
Maximum CTCAE Grade ≥ 3	3 (25)	11 (25)	14 (25)
Patients with any SAE	**2 (17)**	**16 (36)**	**18 (32)**
Patients with any drug-related* SAE	2 (17)	8 (18)	10 (18)
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	**2 (17)**	**3 (7)**	**5 (9)**
Patients with drug-related AE leading to treatment interruption and/or dose reduction	2 (17)	2 (5)	4 (7)
Patients with any AE leading to death	**0**	**2 (5)**	**2 (4)**
Patients with any drug-related AE leading to death	0	0	0

*'Drug-related' refers to investigational drug ICT01-related AEs (of note, the category 'any AE' comprises all emerging adverse events, including unlikely/possible/probably related/not related events).

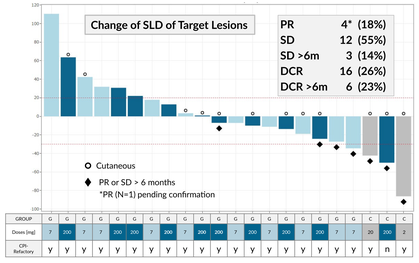
Reasons for treatment discontinuation: pneumonitis (n=1), *possibly/probably related* to ICT01.

Reasons for treatment interruption: immune-related AE (n=2), laboratory abnormalities (n=2), all *possibly/probably related* to ICT01 — laboratory abnormalities (n=2), infection (n=1), gastrointestinal (n=1), hip fracture (n=1), all *unlikely/not related* to ICT01.

Reasons for death: myocarditis and tumor haemorrhage, each n=1, all deaths *unlikely/not related* to ICT01.

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=22)**



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.

Figure 6: **Treatment and response duration to ICT01+pembrolizumab in 2L CPI-refractory or CPI-relapsed metastatic melanoma patients (N=22)**

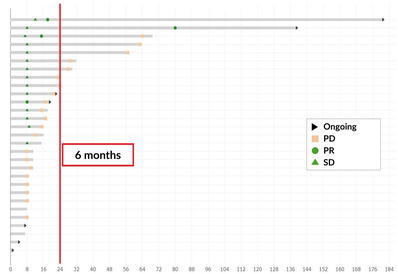


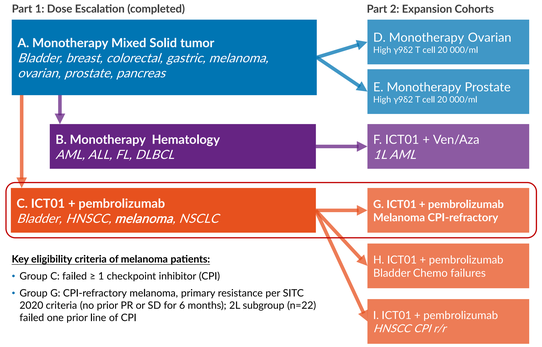
Table3: **Efficacy signal with ICT01+pembrolizumab compares favorably with benchmark studies**

Variables	ICT01+pembrolizumab 2L R/R (n=22)	ICT01+pembrolizumab 2L cutaneous R/R (n=13)	Ipilimumab+nivolumab[1] SWOG S1616 CPI-refractory (no 1L CR or PR) (n=69)	OPDUALAG[2] R/R[1] 2L+ (n=351)	Pembrolizumab +ipilimumab[3] R/R[1] 2L+ (n=70)
EFFICACY					
ORR [%] (CI)	4 (18%) (95%CI, 5-40)	3 (23%) (95%CI, 5-54)	28 (90%CI, 19–38)	12 (95%CI, 7–18)	27 (95% CI, 18–41)
mPFS [months]	4	7	–	2 (95% CI 2–4)	5 (95% CI, 3–8)
PFS 6 months [%] (CI)	6 (27%) (95%CI, 11-50)	5 (38%) (95%CI, 14-68)	34 (90% CI 25–43)	29 (95% CI 24.2–34.1)	–
DoR, median [months] (CI)	NR (95%CI, 16-NR)	NR (95%CI, 16-NR)	41 (90% CI, 8–NR)	NR (12.9–NR)	16 (95% CI, 8–NR)
SAFETY					
Grade ≥ 3 TRAE (%)	9 (40)	5 (38)	50	15	27
AEs leading to discontinuation [n]	1	1	29	5	–

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.

STUDY DESIGN AND METHODS

Figure 3: **EVICTION Phase 1/2a study design**



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

PATIENT CHARACTERISTICS

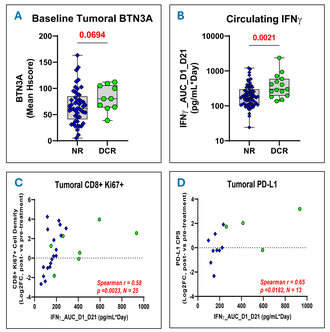
Table 2: **Patient characteristics of 2L melanoma patients treated with ICT01+pembrolizumab**

Variables [n (%)] or [median (range)]	ICT01+pembrolizumab 2L Melanoma N=22	PR N=4	SD 6 m N=3
Age, years	57 (32-88)	64 (53-68)	44 (44-46)
< 65 years	14 (64)	2	3
Subtypes of melanoma			
Cutaneous	12 (55)	3	2
Mucosal	1 (5)		
Acral	2 (9)		
Uveal	2 (9)		
Other/Unknown	5 (23)	1	1
Baseline LDH			
< 2 x ULN	18 (82)	2	3
≥ 2 x ULN*	4 (18)	2	
Presence of liver metastases			
Yes	10 (45)	2	1
No	12 (55)	2	2
Prior (neo)adjuvant immunotherapy	9 (41)	1	1
Prior BRAF/MEK	5 (23)	1	2
Prior metastatic immunotherapy	18 (82)	3	2

Best response of PR or durable SD for 6 months are observed in patients with advanced disease demonstrated by presence of liver metastasis and increased baseline LDH.

BIOMARKER DATA

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)**



Area under the curve (AUC, pg/mL*day) of circulating IFNg 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.
Data shown for all solid tumor patients.

Abbreviations: DCR, disease control rate; NR, no response (best response disease progression).

SUMMARY AND CONCLUSION

- Doses of up to 200 mg ICT01 in combination with pembrolizumab have been shown to be safe and well tolerated (i.e., no dose-limiting toxicities possibly-/probably-related to ICT01 have been reported to date).
- ICT01+pembrolizumab showed a manageable safety profile with asthenia, infusion related reaction and cytokine release syndrome as most frequent AEs and overall rare serious and immune-related AEs.
- ICT01+pembrolizumab demonstrated clinically meaningful anti-tumor efficacy in 2L metastatic melanoma patients with CPI-primary resistant or CPI-relapsed disease.
- A subset of metastatic melanoma patients showed deep and durable anti-tumor responses.
- Anti-tumor response appears to be related to baseline tumoral BTN3A expression, sustained elevation of IFNγ levels, and ICT01-induced tumor immune microenvironment remodeling.

SCAN ME