ICT01 and pembrolizumab in combination elicit deep and durable responses in heavily pretreated patients with urothelial cell carcinoma: **interim results from study EVICTION**

Abstract #641

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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**

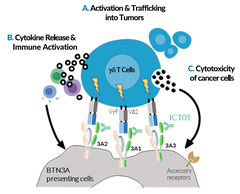

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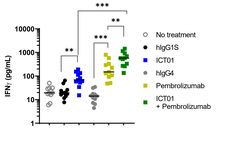
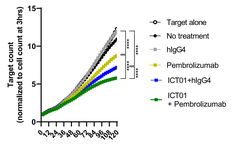
Figure 2: **ICT01 potentiates pembrolizumab anti-tumor activity**



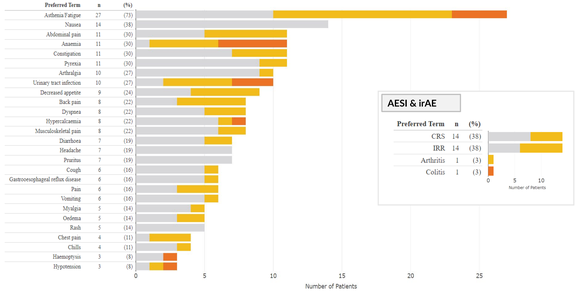
IFNγ in supernatant of human isolated T cells co-cultured with allogenic monocyte-derived dendritic cells in the presence of indicated antibodies *** p<0.001, ** p<0.01.



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 UCC patients (or Grade ≥ 3) treated with ICT01+pembrolizumab (N=37)**



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 (73%), infusion related reaction (IRR, 38%), cytokine release syndrome (CRS, 38%) and nausea (38%). Serious TRAEs (Grade ≥ 3) and immune-related AEs (Grade ≥ 2) were overall rare.

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

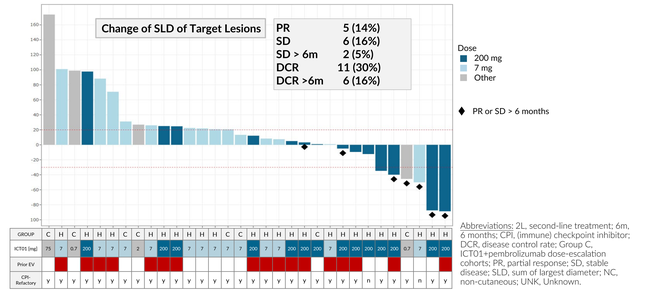
AE category [n (%)]	ICT01+pembrolizumab Group C (N=9)	Group H (N=28)	Pooled (N=37)
Patients with any AE	**9 (100)**	**28 (97)**	**37 (100)**
Maximum CTCAE Grade 1		2 (7)	2 (5)
Maximum CTCAE Grade 2	3 (33)	15 (54)	18 (49)
Maximum CTCAE Grade 3	6 (67)	10 (36)	16 (43)
Maximum CTCAE Grade 4			
Maximum CTCAE Grade 5		1 (4)	1 (3)
Patients with any drug-related* AE	**9 (100)**	**27 (96)**	**36 (97)**
Maximum CTCAE Grade ≥ 3	1 (11)	4 (14)	5 (14)
Patients with any SAE	**5 (56)**	**13 (46)**	**18 (49)**
Patients with any drug-related* SAE	1 (11)	9 (32)	10 (27)
Patients with any AE leading to permanent study discontinuation	**0**	**0**	**0**
Patients with any drug-related AE leading to permanent study discontinuation	0	0	0
Patients with any AE leading to treatment interruption and/or dose reduction	**0**	**7 (25)**	**7 (19)**
Patients with drug-related AE leading to treatment interruption and/or dose reduction	0	4 (14)	4 (11)
Patients with any AE leading to death	**0**	**0**	**0**
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: immune-related AE (n=2), musculoskeletal (n=2), all possibly/probably related to ICT01 — laboratory abnormalities (n=2), infection (n=4), gastrointestinal (n=1), other (n=3), all unlikely/not related to ICT01.

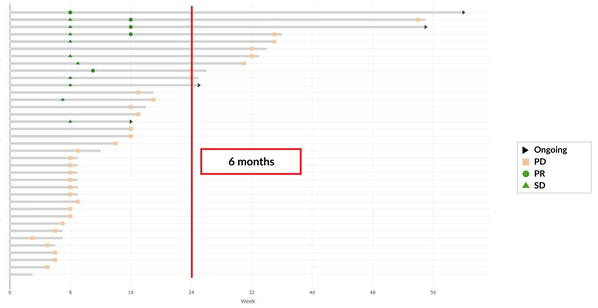
EFFICACY OF ICT01 + PEMBROLIZUMAB IN UCC PATIENTS

Figure 5: **Anti-tumor efficacy of ICT01+pembrolizumab in UCC patients *(cut-off date: September 12, 2024; N=37)***



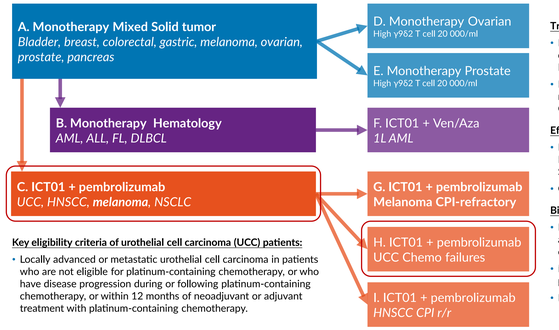
Abbreviations: 2L, second-line treatment; 6m, 6 months; CPI, (immune) checkpoint inhibitor; DCR, disease control rate; Group C, ICT01+pembrolizumab dose-escalation cohorts; PR, partial response; SD, stable disease; SLD, sum of largest diameter; NC, non-cutaneous; UNK, Unknown.

Figure 6: **Treatment and response duration in UCC patients treated with ICT01+pembrolizumab**



STUDY DESIGN AND METHODS

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



Key eligibility criteria of urothelial cell carcinoma (UCC) patients:

- Locally advanced or metastatic urothelial cell carcinoma in patients who are not eligible for platinum-containing chemotherapy, or who have disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

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 demographics and antitumor responses in UCC**
Responders to ICT01+pembrolizumab had visceral disease and prior CPI and/or enfortumab vedotin

Variables [n (%)] or [median (range)]	ICT01+pembrolizumab (Group C&H) Total N=37	PR N=2	SD 6 m N=2
Location of metastases			
Lymph Node only	2 (5)		
Visceral disease	36 (97)	5/36 (14)	2/36 (6)
Bone metastases	12 (32)		2/12 (17)
Presence of liver metastases			
Yes	12 (32)	2/12 (17)	2/12 (17)
No	25 (68)	3/25 (12)	
Lines of prior therapy			
< 3 lines	5 (14)	1/5 (20)	
≥ 3 lines	32 (86)	4/32 (12)	2/32 (6)
Prior (neo)adjuvant immunotherapy			
Chemotherapy or ADC	19 (51)	2/19 (10)	2/19 (10)
Immunotherapy	3 (8)	1/4 (25)	
Prior palliative immunotherapy			
Chemotherapy systemic	27 (73)	3/27 (11)	2/27 (7)
Enfortumab vedotin	19 (50)	3/19 (16)	2/19 (10)
Immunotherapy	32 (86)	3/32 (9)	2/32 (6)
Targeted therapy	5 (14)		1 /5 (20)

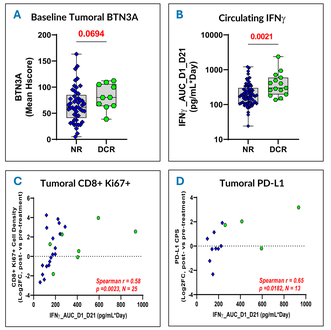
Best response of PR or durable SD for 6 months were observed in patients with advanced disease as demonstrated by the presence of visceral disease and liver metastases.

Also, among the responders were patients pre-treated with enfortumab-vedotin and immunotherapy.

Abbreviations:
ADC Antibody Drug Conjugate; CPI, (immune) checkpoint inhibitor; ICT01$^{low/high}$, 7 mg/200 mg ICT01 Q3W; PEM, pembrolizumab; PR, partial Response; SD Stable Disease.

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

- ICT01 in combination with pembrolizumab has 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 in combination with pembrolizumab demonstrates efficacy data in advanced metastatic UCC.
- DCR is related to baseline tumoral BTN3A expression, sustained elevation of IFNg levels, and expression of markers of tumor microenvironment remodeling.

Doses of ICT01 up to 200 mg in combination with pembrolizumab are safe and well tolerated, and induced deep and durable anti-tumor responses in select patients with difficult-to-treat tumor disease. ICT01 in combination with pembrolizumab generated clinically meaningful anti-tumor efficacy in advanced metastatic UCC.

SCAN ME