

PROTA - A phase I clinical trial combining an oncolytic adenovirus encoding for TNFa and IL-2 with pembrolizumab for the treatment of platinum-resistant or -refractory ovarian cancer

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Background

Platinum-resistant or -refractory ovarian cancer disease has poor prognosis and **limited effective treatment options**;

While the ovarian tumor microenvironment can demonstrate a vast array of potential immunological targets for therapy, **no immunotherapy has been approved for this indication, including immune checkpoint inhibitors**;

While single-agent pembrolizumab (an anti-PD-1 monoclonal antibody) demonstrated a low response rate in platinum-resistant ovarian cancer (as reported in the KEYNOTE-100 phase II trial), **long-term responders were observed, opening avenues for improvement**;

Igrelimogene litadenorepvec (Ad5/3-E2F-d24-hTNF-ires-hIL2; TILT-123), a chimeric serotype oncolytic adenovirus encoding tumor necrosis factor alpha (TNFa) and interleukin-2 (IL-2), lyses tumor cells and is capable of recruiting and activating T-cells in the tumor, via inherent virus properties and local IL-2/TNFa production;

TILT-123 may improve the activity of pembrolizumab, owing to complementary mechanisms of action: 1) virus-induced direct tumor lysis and increase of intratumoral activated T-cells, and 2) protection of T-cell exhaustion via PD-1 blockade;

The PROTA phase I clinical study (**NCT05271318**) was established to assess the safety of **TILT-123 and pembrolizumab** in participants with **platinum-resistant or -refractory ovarian cancer disease**

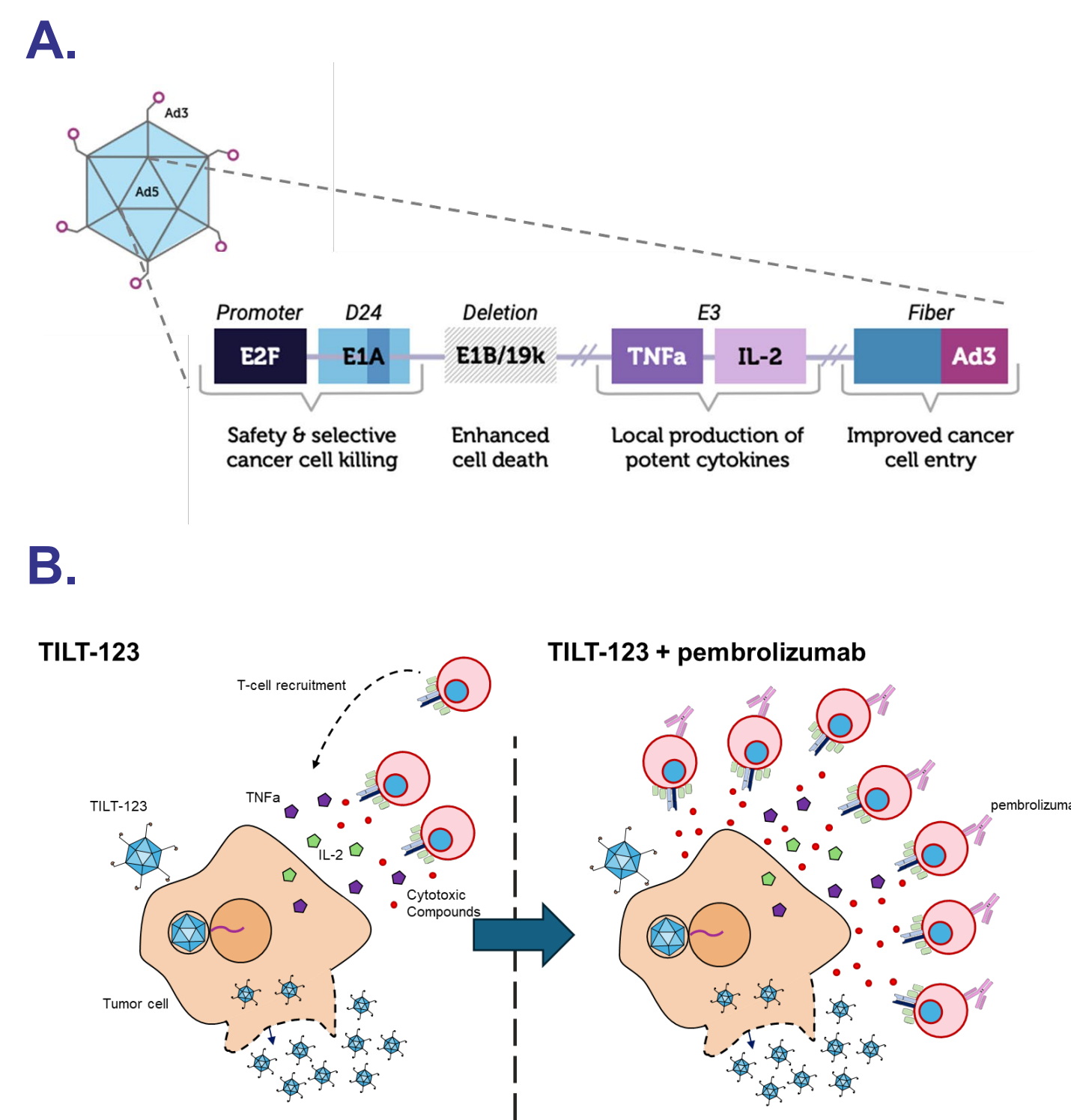


Figure 1 – (A) TILT-123 genetic structure and (B) mode of action of TILT-123 and Pembrolizumab.

Methods

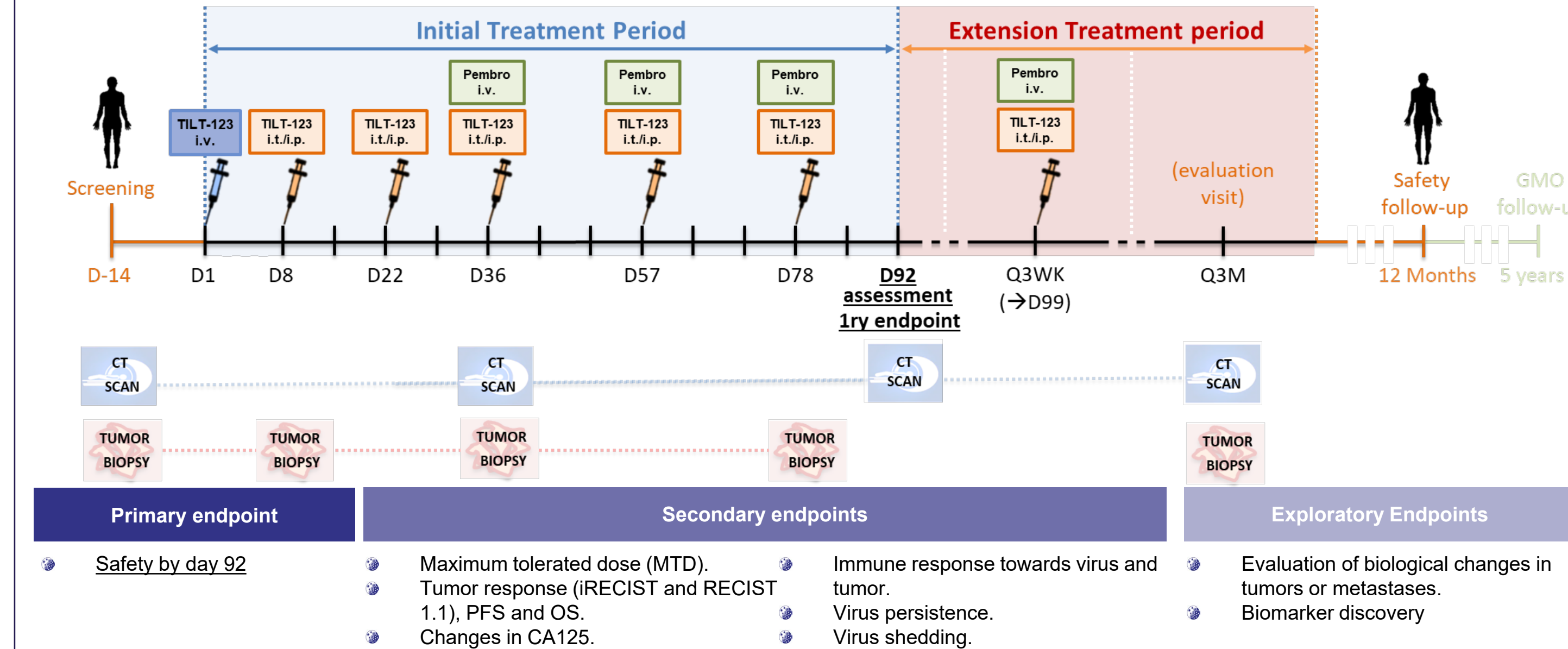


Figure 2 – TILT-T563 simplified clinical trial protocol.

- This is an open label phase I clinical trial using a standard 3+3 dose-escalation scheme;
- Participants needed to have at least one tumor (>14 mm in diameter) or carcinomatosis available for local virus injection (intratumoral and/or intraperitoneal);
- Each patient receives one intravenous injection of TILT-123, throughout the trial;
- Intratumoral/intraperitoneal injections of TILT-123, throughout the trial;
- Pembrolizumab was given from day 36 on, at the standard 200mg every 3 weeks, and TILT-123 doses were escalated and administered according to table 1;
- TILT-T563 phase 1 dose-escalation study enrolled patients at Mayo Clinic, Rochester, MN, USA and Docrates Cancer Center, Helsinki, Finland.

Table 1 – Dose and frequency of TILT-123 and Pembrolizumab.

Cohort #	TILT-123		Pembrolizumab
	I.V.	I.V./i.p.	
1	Day 1, 8, 22, 36, Q3wk	1x10 ¹¹	Q3wk
2	3x10 ¹¹	1x10 ¹¹	200 mg
3	1x10 ¹²	3x10 ¹¹	
4	2x10 ¹²	3x10 ¹¹	
5	4x10 ¹²	5x10 ¹¹	

1 Demographics and Safety

Table 2 – Key Demographics in the dose-escalation study. Data cut-off 4th of April 2024. The results have not been fully monitored, audited or verified by the quality assurance.

Parameter	Total (n/pts)
Age at Enrollment (years)	Median 66
Performance Status	0 5 1 10
Ovarian Cancer Type	Fallopian tube 3 Epithelial 9 Primary Peritoneal 3
Prior Cancer therapies	2 (13%)
Median number of previous systemic treatment lines	7
Platinum Status	Resistant 8 Refractory 7

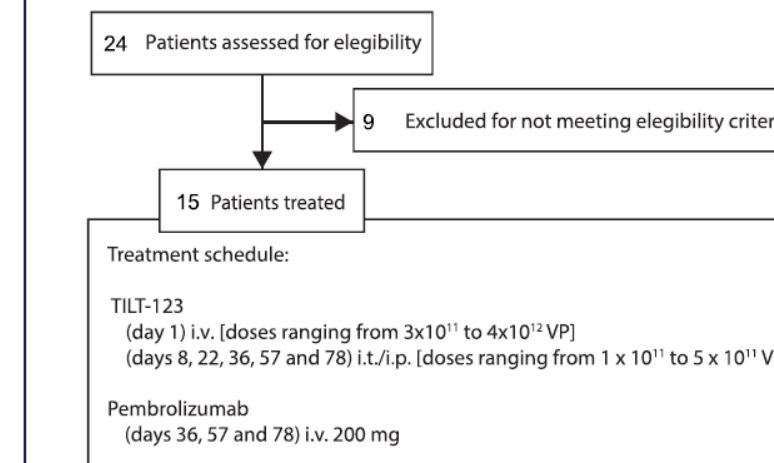


Figure 3 – Consort Diagram. Data cut-off 4th April 2024. The results have not been fully monitored, audited or verified by the quality assurance.

Table 3 – Treatment-related adverse events as judged by the investigators in the dose-escalation study. Data cut-off 4th of April 2024. Adverse events graded based on the Common Terminology Criteria for Adverse Events (CTCAE). The results have not been fully monitored, audited or verified by the quality assurance.

Lowest level Term	Grade 1, n* (% of patients)	Grade 2, n* (% of patients)	Grade 3, n* (% of patients)	Grade 4, n* (% of patients)	Any grade, n* (% of patients)
Anemia	8 (42%)	5 (26%)			13 (68%)
Fatigue	1 (7%)	2 (13%)			3 (20%)
hyperkalemia	1 (7%)				1 (7%)
abdominal discomfort	1 (7%)	1 (7%)			2 (13%)
nausea	9 (46%)	1 (7%)			10 (53%)
anorexia	6 (33%)				6 (33%)
infusion site reaction	1 (7%)				1 (7%)
abdominal pain	1 (7%)				1 (7%)
vomiting	4 (20%)				4 (20%)
lymphocyte count decreased	6 (27%)	9 (27%)	12 (33%)	4 (27%)	31 (83%)
fever	2 (13%)				2 (13%)
Headache	8 (40%)	2 (13%)			10 (47%)
Diarrhea	2 (13%)				2 (13%)
Chills	3 (20%)	2 (13%)			5 (27%)
alopecia	11 (33%)	1 (7%)			12 (33%)
skin rash	2 (13%)		1 (7%)	1 (7%)	4 (20%)
Flu-like symptoms	2 (7%)				2 (7%)
Pyrexia	1 (7%)				1 (7%)
Cough	1 (7%)				1 (7%)
Intermittent Shortness of Breath	1 (7%)		1 (7%)		2 (13%)
Dyspnea	1 (7%)				1 (7%)
right pelvic pain		1 (7%)			1 (7%)
hemiparesis			1 (7%)		1 (7%)
Mucositis oral	1 (7%)				1 (7%)
Abdominal bloating	1 (7%)				1 (7%)
creatinine increased	3 (7%)				3 (7%)
elevated neutrophils	2 (7%)				2 (7%)
elevated platelet count	1 (7%)				1 (7%)
Worsening fatigue	1 (7%)				1 (7%)
Loose Stools	1 (7%)				1 (7%)
Abdominal pain increased	1 (7%)				1 (7%)

- Patients enrolled had received a high number of cancer therapies before enrolling into the trial;
- WHO/ECOG performance status was mostly 1;
- Epithelial ovarian cancer was the most prevalent tumor type in this dose-escalation study;
- The most frequent AEs (>30%) were fever, lymphocyte count decrease, fatigue, nausea, anemia, anorexia, chills (mostly low grade);
- No treatment-related grade 5 AEs;
- Two grade 3 serious unexpected AEs related to treatment;
- No dose-limiting toxicities were seen.

2 Anti-tumor Activity

Table 4 – Antitumor response by patient based on CT imaging, serum markers, and overall survival. Data cut-off 4th April 2024. PD – Progressive disease, SD – Stable Disease, PR – Partial response, N/A – not applicable, *Patient still alive as of the data cut-off. The results have not been fully monitored, audited or verified by the quality assurance.

Patient ID	Cohort	Age	ECOG status at baseline	Cancer type	Histological Subtype	Median Number of previous systemic treatments	Platinum status	Best Overall response RECIST 1.1	Best Overall response RECIST	Best CA125 change (compared to baseline), d = day	OS (days)
302-05	1	60	1	Fallopian tube cancer	HGSOC	7	Resistant	PD	iUPD	-8.1%, d8	85
302-06	1	70	1	Epithelial ovarian cancer	LGSOC	12	Resistant	SD	ISD	-37.5%, d36	306
301-01	1	71	1	Primary peritoneal cancer	Serous	4	Resistant	SD	ISD	+112.2%, d8	77
301-02	2	61	1	Epithelial ovarian cancer	HGSOC	3	Resistant	SD	ISD	+27.9%, d8	434
301-03	2	72	1	Epithelial ovarian cancer	Serous adenocarcinoma	12	Resistant	SD	ISD	-6.4%, d8	122
301-04	2	58	1	Epithelial ovarian cancer	Serous	7	Resistant	PD	iUPD	+24.9%, d36	93
302-07	3	66	1	Fallopian tube cancer	HGSOC	5	Refractory	SD	ISD	+30.7%, d8	190
301-05	3	78	0	Epithelial ovarian cancer	HGSOC	1	Resistant	SD	ISD	+8.5%, d8	369*
302-09	3	51	1	Epithelial ovarian cancer	HGSOC	8	Refractory	PD	iUPD	-14.8%, d57	280
302-10	4	54	0	Epithelial ovarian cancer	HGSOC	10	Refractory	SD	ISD	-28.2%, d98	160*
301-10	4	58	0	Fallopian tube cancer	HGSOC	5	Resistant	PD	iUPD	+56.1%, d8	151*
302-11	4	36	1	Primary peritoneal cancer	Adenocarcinoma LGSOC	9	Refractory	N/A	N/A	+26.1%, d8	149
301-11	4	69	1	Epithelial ovarian cancer	Mucinous carcinoma	2	Refractory	PR	iPR	-50.0%, d159	130*
301-12	4	73	0	Epithelial ovarian cancer	Carcinosarcoma	3	Refractory	SD	ISD	+3.8%, d8	123
302-12	4	71	0	Primary peritoneal cancer	HGSOC	8	Refractory	PD	iUPD	-34.5%, d36	97

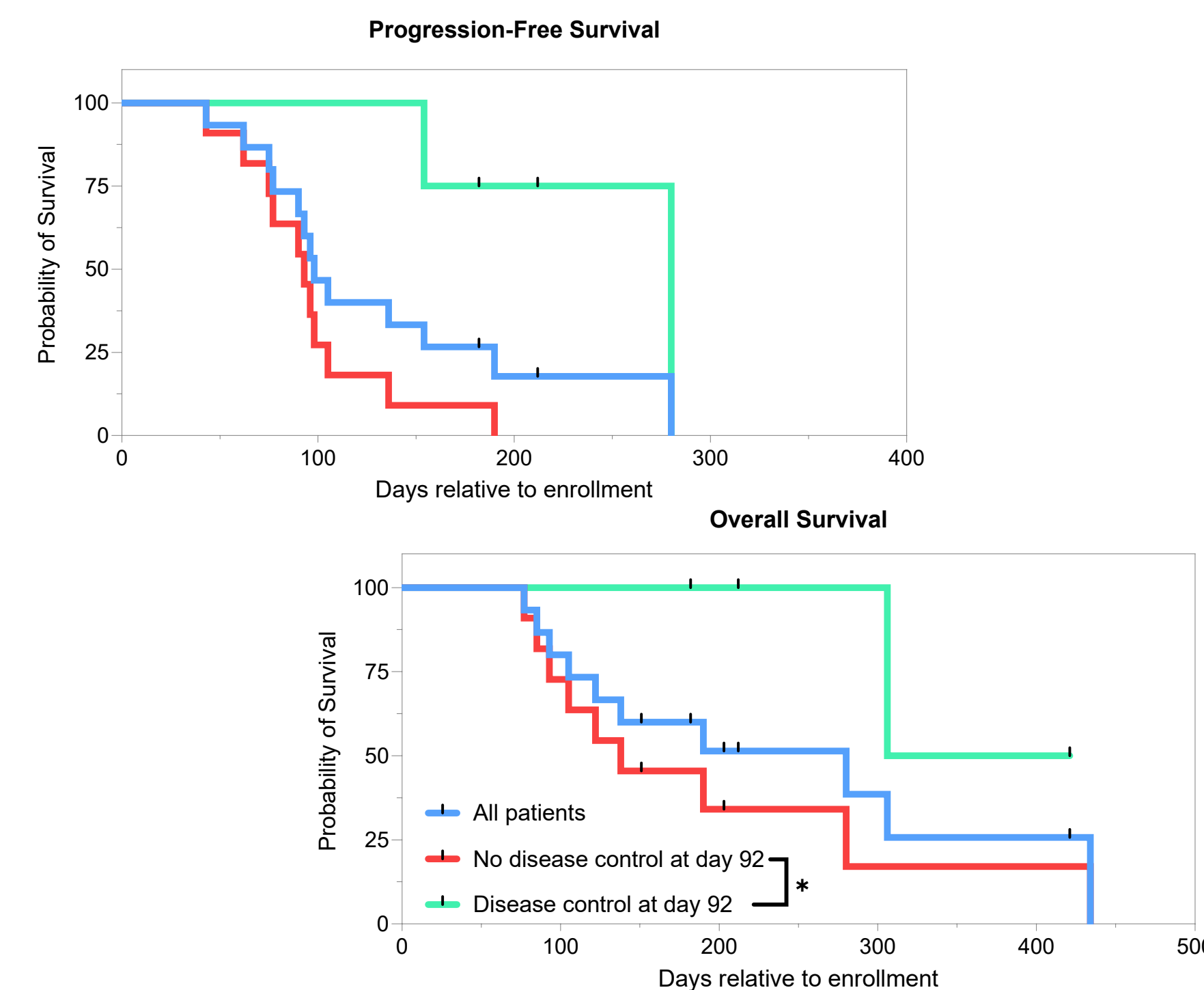


Figure 4 – Progression-Free Survival and Overall survival in patients enrolled in the trial. Data cut-off 04th April 2024. The results have not been fully monitored, audited or verified by the quality assurance. *p<0.05

After TILT-123 + Pembrolizumab treatment

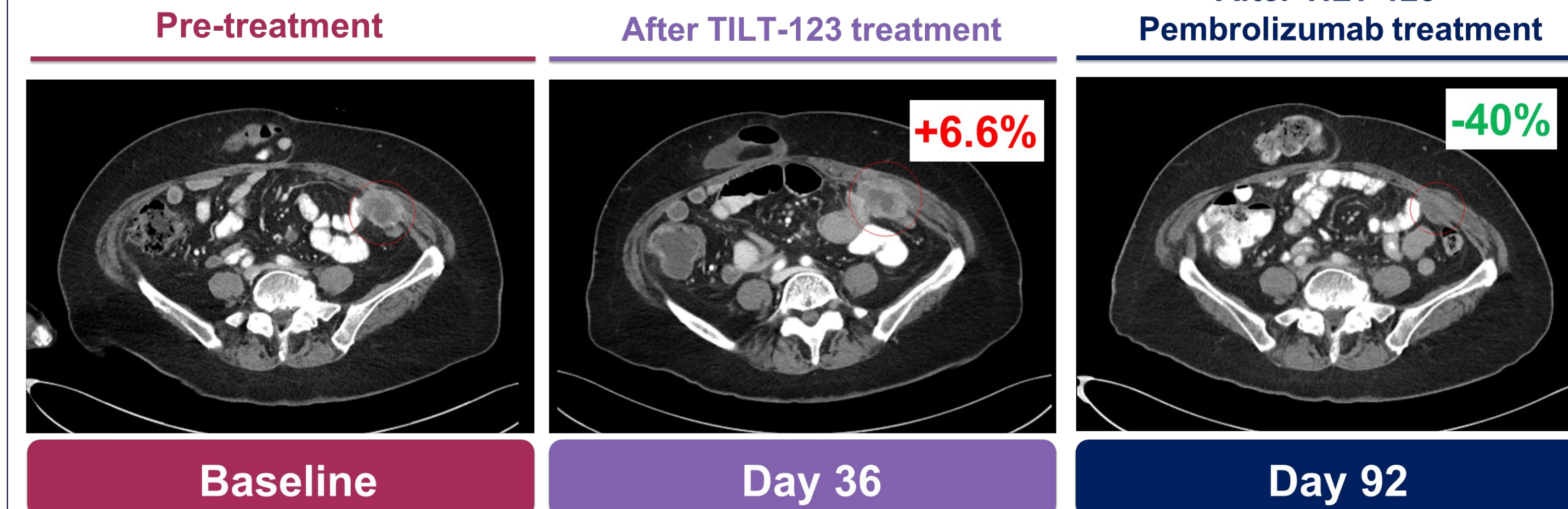
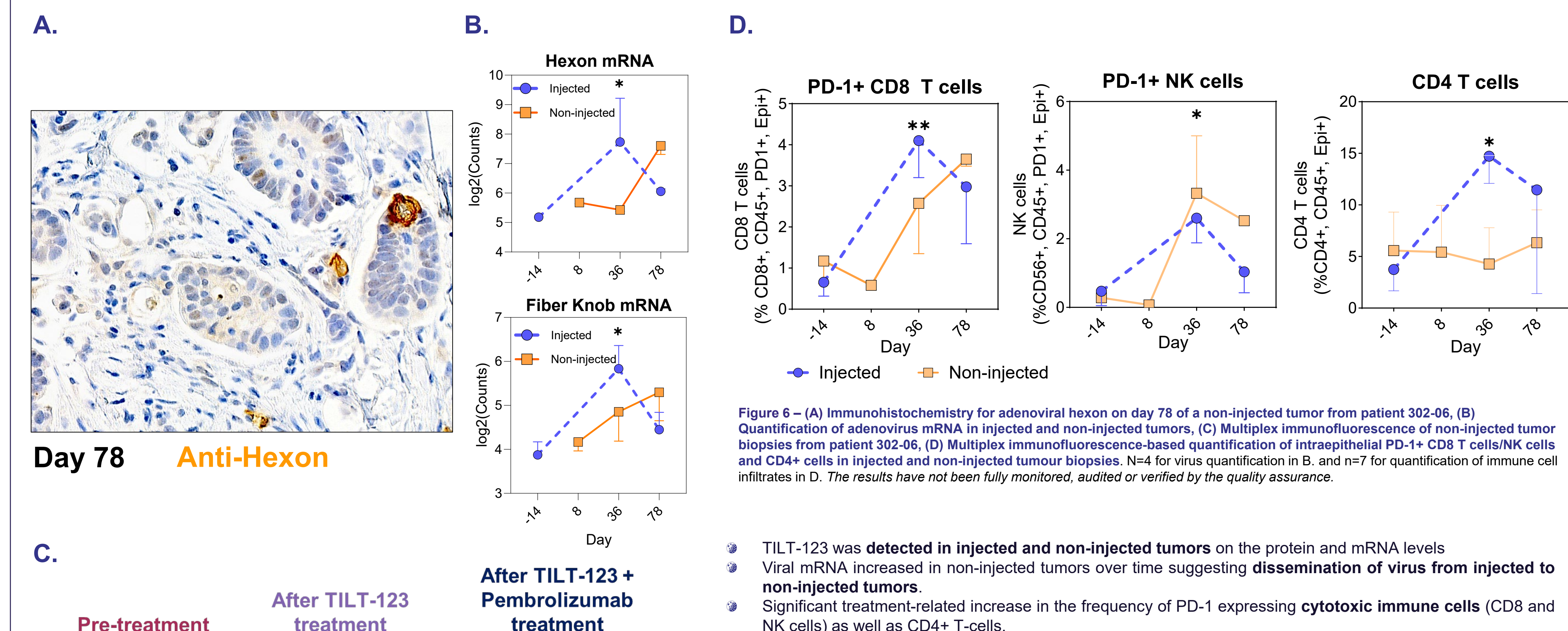


Figure 5 – CT images of injected abdominal wall metastasis in patient 301-11 with mucinous ovarian cancer. Data cut-off 4th April 2024. The results have not been fully monitored, audited or verified by the quality assurance.

- Disease control was achieved in 64.3% of patients evaluable by RECIST1.1
- Median PFS and OS in all patients were 98 and 280 days, respectively;
- In patients with SD or better on day 92 by RECIST1.1, median OS was 363.5 days and median PFS was 280 days;
- 4 out of 15 treated patients are still alive at the data cut-off date;
- CA125 decreased below baseline in 50% of patients**;
- Therapy with TILT-123 and Pembrolizumab led to a Partial Response including the reduction of 40% of one of the target lesions, as indicated in the figure 3 example;
- ORR by RECIST 1.1 was 7.7% (1/14) in all evaluable patients and 20% (1/5) in highest dose cohort 4 This patient had received carboplatin + paclitaxel and capecitabine + oxaliplatin prior to enrolling into the study;
- Patient remains in treatment;

3 Virus Presence and T-cell infiltration



- TILT-123 was **detected in injected and non-injected tumors** on the protein and mRNA levels
- Viral mRNA increased in non-injected tumors over time suggesting **dissemination of virus from injected to non-injected tumors**.
- Significant treatment-related increase in the frequency of PD-1 expressing **cytotoxic immune cells** (CD8 and NK cells) as well as CD4+ T-cells.

Conclusions

- The combination of TILT-123 and pembrolizumab is **safe** in platinum-resistant and -refractory ovarian cancer;
- The safety profile is consistent with other virus-based immunotherapies;
- Disease control seen in heavily pretreated patients by RECIST 1.1 and CA125 analysis;
- Long lasting PR in a patient with mucosal ovarian cancer
- Long PFS and OS in a subpopulation of patients
- TILT-123 is able to reach non-injected tumors and cause extensive immunomodulation;
- Investigation of TILT-123, pembrolizumab and pegylated liposomal doxorubicin is ongoing in similar but less heavily pre-treated patients

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