Phase 1/2 Dose Escalation and Dose Expansion Study of TransCon IL-2 β/γ Alone or in Combination with Pembrolizumab: Determination of Recommended Phase 2 Dose (RP2D)

Poster Presentation: ESMO 2023
October 23, 2023

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This presentation contains forward-looking statements. All statements other than statements of historical facts contained in this presentation, such as statements regarding our prospective product candidates; clinical trial results; the expected timing of future clinical trial results; the scope, progress, results and costs of developing our product candidates or any other future product candidates; timing and likelihood of success; plans and objectives of management for future operations; and future results of current and anticipated products and product candidates are forward-looking statements. These forward-looking statements are based on our current expectations and beliefs, as well as assumptions concerning future events. These statements involve known and unknown risks, uncertainties and other factors that could cause our actual results to differ materially from the results discussed in the forward-looking statements. These risks, uncertainties and other factors are more fully described in our reports filed with or submitted to the Securities and Exchange Commission, including, without limitation, our most recent Annual Report on Form 20-F filed with the SEC on February 16, 2023 particularly in the sections titled “Risk Factors” and “Operating and Financial Review and Prospects.” In light of the significant uncertainties in our forward-looking statements, you should not place undue reliance on these statements or regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified timeframe, or at all.

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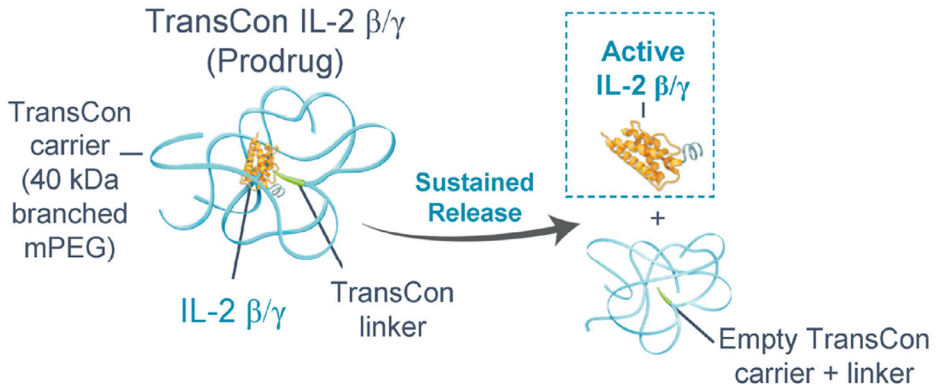
Background

- TransCon IL-2 β/γ, an investigational novel prodrug with sustained release of a receptor-selective IL-2 (IL-2 β/γ), was designed to address drawbacks of aldesleukin: potent activation of undesired IL-2Rα+ cell types and suboptimal pharmacokinetics (PK) characterized by high Cmax and short half-life[1]
- TransCon IL-2 β/γ is created by permanently attaching a 5 kDa mPEG in the IL-2Rα binding site to achieve IL-2Rβ/γ bias. A 40 kDa mPEG carrier is transiently attached to IL-2 β/γ to create a prodrug, TransCon IL-2 β/γ. This results in a lower Cmax and significantly prolonged half-life of released IL-2 β/γ compared to aldesleukin[1]



1. Rosen DB, et al. J *Immunother Cancer.* 2022;10:e004991.

TransCon IL-2 β/γ Phase 1 Trial Dose Escalation

Parts 1 and 2: Dose Escalation (3+3 Design)

Part 1
Monotherapy dose-escalation in advanced solid tumors with no other SOC options

- Any line of therapy, any solid tumor
- Optional choice to add pembro upon disease progression

20 µg/kg
n=4; no DLTs

40 µg/kg
n=3; no DLTs

80 µg/kg
n=5; no DLTs

RP2D
120 µg/kg
n=8, no DLTs

160 µg/kg
n=5, 1 DLT

Part 2
Dose-escalation in combination with pembrolizumab in advanced solid tumors

- Indications where pembro monotherapy has known clinical activity
- No more than 2 lines of prior metastatic treatment

20 µg/kg + pembro
n=4; no DLTs

40 µg/kg + pembro
n=5; no DLTs

80 µg/kg + pembro
n=5; no DLTs

RP2D
120 µg/kg + pembro
n=7; no DLTs

Part 3: Indication-Specific Dose Expansions Cohorts at RP2D

Cohort 3
TransCon IL-2 β/γ + chemo
PROC
n = ~29 + 27

Cohort 4
TransCon IL-2 β/γ + TransCon TLR 7/8 Agonist
Post anti-PD-1 Melanoma
n= ~22+19

Cohort 5
TransCon IL-2 β/γ + TransCon TLR 7/8 Agonist
2L+ Cervical Cancer
n= ~26+15

Cohort 6a
TransCon IL-2 β/γ monotherapy
Neoadjuvant Melanoma
n= ~17+19

Cohort 6b
TransCon IL-2 β/γ + pembro
Neoadjuvant Melanoma
n= ~17+19

Cohort 6c
TransCon IL-2 β/γ + TransCon TLR 7/8 Agonist
Neoadjuvant Melanoma
n= ~17+19

Cohort 7
TransCon IL-2 β/γ + chemo + pembro
Neoadjuvant NSCLC
n= ~22+18

Key efficacy endpoints:

- Cohorts 3, 4, and 5: ORR and DoR
- Cohorts 6a-6c and 7 (Neoadjuvant): pCR

Sample sizes based on Simon's 2-stage design

The dose reflected is in IL-2 equivalents. Black box around Cohorts 6a-c indicates randomized enrollment. Cohorts with dashed border in Part 3 are not currently open. Data cut-off for all Parts 1 and 2 was 15 August 2023. pembro, pembrolizumab; DLT, dose limiting toxicity during first cycle of 21 days; RP2D, recommended phase 2 dose.

IL Trial Believe

TransCon IL-2 β/γ monotherapy/combination RP2D was determined to be 120 µg/kg

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TransCon IL-2 β/γ Demographics and Clinical Characteristics

Dose Escalation Demographics	Monotherapy Part 1 N=25	Combination Part 2 N=21
Age (years), median (min, max)	**64 (37, 82)**	**61 (35, 79)**
Sex		
Male	**8**	**8**
Female	**17**	**13**
Prior Anti-PD-1/L1 Therapy (n %)	**9 (36)**	**8 (38)**
Prior lines of systemic therapies Median (min, max)	**4 (1,15)**	**2 (1,3)**
Tumor Types		
HNSCC	**5**	**2**
CRC	**3**	**1**
SCLC	**1**	**3**
Ovarian	**3**	**0**
Pancreas	**3**	**0**
Endometrial	**1**	**2**
Cholangiocarcinoma	**1**	**2**
Cervical	**0**	**3**
Triple-negative breast cancer	**2**	**0**
Esophageal	**1**	**1**
NSCLC	**0**	**2**
Invasive ductal carcinoma (breast)	**1**	**0**
Leiomyosarcoma	**1**	**0**
Renal	**1**	**0**
Uterine leiomyosarcoma	**1**	**0**
Rectal	**1**	**0**
Acinic Cell Carcinoma	**0**	**1**
Adenoid Cystic Carcinoma	**0**	**1**
Vulvar	**0**	**1**
Nasopharyngeal	**0**	**1**
Adrenocortical Carcinoma	**0**	**1**

HNSCC, head and neck squamous cell carcinoma; CRC, colorectal cancer; NSCLC= Non-small cell lung cancer; SCLC, small cell lung cancer.

Data cut 15 Aug 2023

Safety and Tolerability

- One dose limiting toxicity (DLT) G3 Worsening CRS occurred in Part 1, Monotherapy, Dose Level 160 µg/kg
- One patient in Part 1, Monotherapy, Dose Level 120 µg/kg experienced a Grade ≥3 treatment-emergent adverse event (TEAE) related to TransCon IL-2 β/γ, Grade(G)3 cytokine release syndrome (CRS)
- One patient in Part 2, Combination Therapy, Dose Level 120 µg/kg experienced Grade ≥3 TEAEs related to TransCon IL-2 β/γ, G3 nausea and G3 vomiting

TransCon IL-2 β/γ
Safety Overview of Part 1 - Monotherapy Dose Escalation

Events	Dose (µg/kg)				
	20 N=4 n (%)	40 N=3 n (%)	80 N=5 n (%)	120 N=8 n (%)	160 N=5 n (%)
DLT	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**1 (20)** *(1) G3 Worsening CRS*
Grade ≥3 TEAEs related to TransCon IL-2 β/γ	**1 (25)** *(1) G4 lymphopenia not clinically significant*	**0 (0)**	**0 (0)**	**1 (12.5)** *(1) G3 CRS*	**4 (80)** *(1) G3 Hypoxia* *(2) G3 Worsening CRS* *(3) G3 Anemia, G3 Thrombocytopenia* *(4) G3 Neutropenia*
Serious TEAEs related to TransCon IL-2 β/γ	**0 (0)**	**0 (0)**	**2 (40)** *(1) G2 CRS* *(2) G2 Tachycardia*	**2 (25)** *(1) G2 CRS* *(2) G3 CRS*	**3 (60)** *(1) G2 Fever, G1 Rash, G3 Hypoxia, G2 Atrial Fibrillation* *(2) G2 Capillary Leak Syndrome* *(3) G3 Worsening CRS*
TEAEs leading to dose reduction	**0 (0)**	**0 (0)**	**2 (40)** *(1) G2 CRS* *(2) G2 Flu-like symptoms*	**3 (37.5)** *(1) G2 CRS* *(2) G3 CRS* *(3) G2 Vomiting*	**2 (40)** *(1) G3 Thrombocytopenia* *(2) G2 Capillary Leak Syndrome*
TEAEs leading to treatment discontinuation	**0 (0)**	**0 (0)**	**0 (0)**	**2 (25)** *(1) G1 CRS related* *(2) G4 Severe septic shock not related to study drug*	**0 (0)**
TEAEs leading to death	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**

CRS, cytokine release syndrome; DLT, dose limiting toxicity during first cycle of 21 days; G, grade; TEAE, treatment-emergent adverse event.

Data cut 15 Aug 2023

IL Trial Believe

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TransCon IL-2 β/γ
Safety Overview of Part 2 - Combination with Pembrolizumab Dose Escalation

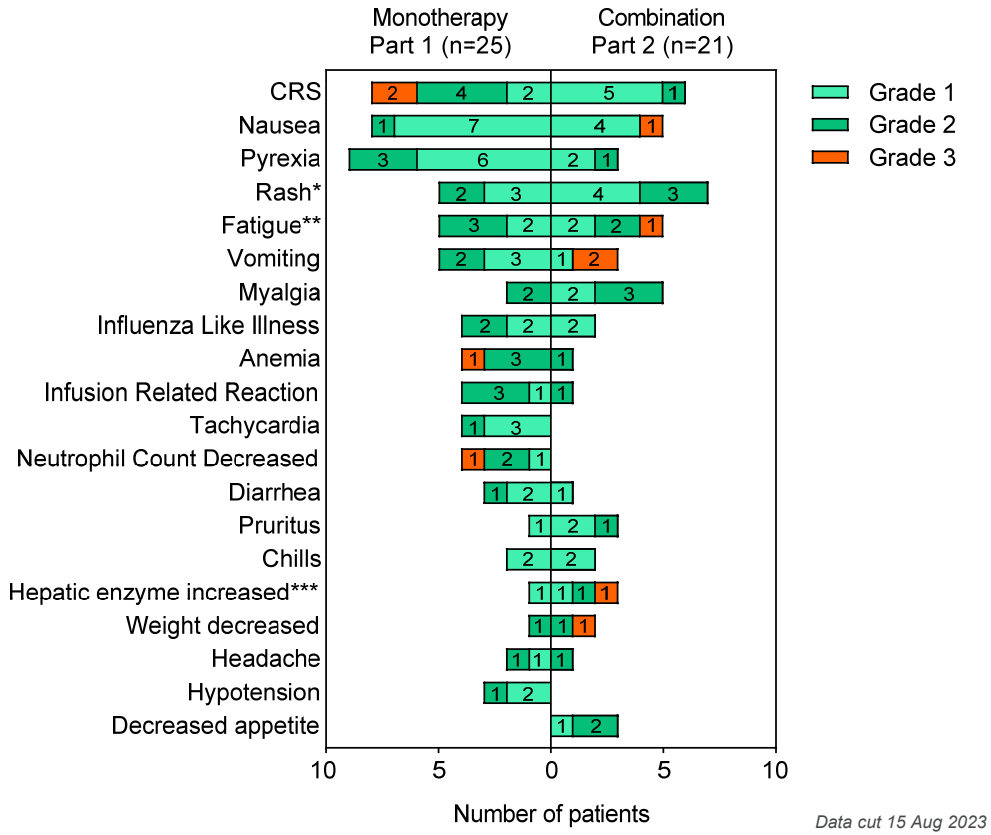
Events	Dose (µg/kg)			
	20 N=4 n (%)	40 N=5 n (%)	80 N=5 n (%)	120 N=7 n (%)
DLT	0 (0)	0 (0)	0 (0)	0 (0)
Grade ≥3 TEAEs related to TransCon IL-2 β/γ	1 (25) *G3 Elevated AST**	1 (20) *G3 Fatigue, G3 Vomiting, G3 Weight decrease*	0 (0)	1 (14.3) *G3 Nausea, G3 Vomiting*
Serious TEAEs related to TransCon IL-2 β/γ	0 (0)	1 (20) *G3 Fatigue, G3 Vomiting, G3 Weight decrease*	0 (0)	1 (14.3) *G3 Nausea, G3 Vomiting, G2 CRS, G2 Worsening gout*
TEAEs leading to dose reduction of TransCon IL-2 β/γ	0 (0)	0 (0)	1 (20) *G2 Hepatitis*	1 (14.3) *G1 CRS*
TEAEs leading to treatment discontinuation of TransCon IL-2 β/γ	0 (0)	0 (0)	0 (0)	1 (4.8) *G1 CRS*
TEAEs leading to death	0 (0)	0 (0)	0 (0)	0 (0)

Data cut 15 Aug 2023

**Subject with known liver metastases*

AST, Aspartate transaminase; G, grade; TEAE, treatment-emergent adverse event.

TEAEs Related to TransCon IL-2 β/γ With >5% Occurrence for All Patients



Data cut 15 Aug 2023

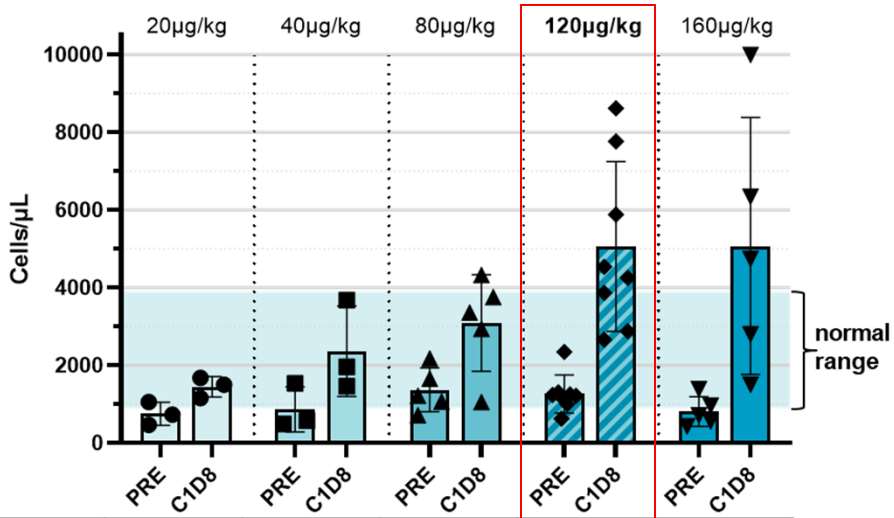
*Rash also includes the reported term 'Rash maculo-popular'
**Fatigue also included the reported term 'Asthenia'
***Hepatic enzyme increased included the reported terms 'AST and ALT increased'

Pharmacokinetics and Pharmacodynamics

- PK data showed dose dependent systemic exposure with a half-life of TransCon IL-2 β/γ of ~37 hours
- Pharmacodynamics (PD) data showed that TransCon IL-2 β/γ induces dose dependent lymphocyte expansion without expanding eosinophils
- PD effects were comparable between Part 1 and 2, with 120 µg/kg showing increased lymphocyte counts above the normal range, supporting this dose as RP2D for monotherapy and combination therapy
- PD data suggested sustained activation and dose dependent expansion of cytotoxic effector cells while regulatory T cells (T_{regs}) were expanded only minimally

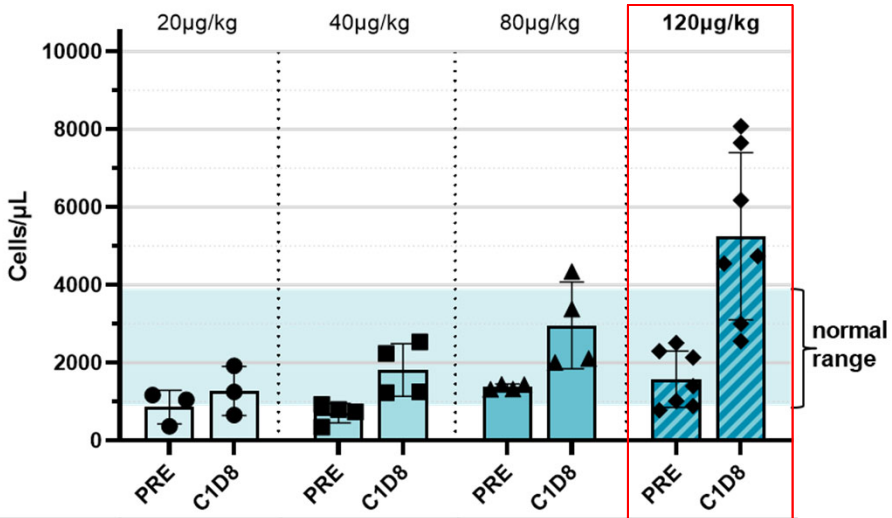
Dose Dependent Lymphocyte Expansion

Absolute Lymphocyte Counts: TransCon IL-2 β/γ Monotherapy



Lymphocytes (cells/mL)	20 µg/kg (n=3)	40 µg/kg (n=3)	80 µg/kg (n=5)	120 µg/kg (n=8)	160 µg/kg (n=5)
median pre-dose	730	580	1220	1230	710
median 7 days post dose	**1500**	**1960**	**3360**	**4395**	**4740**

Absolute Lymphocyte Counts: TransCon IL-2 β/γ + Pembro

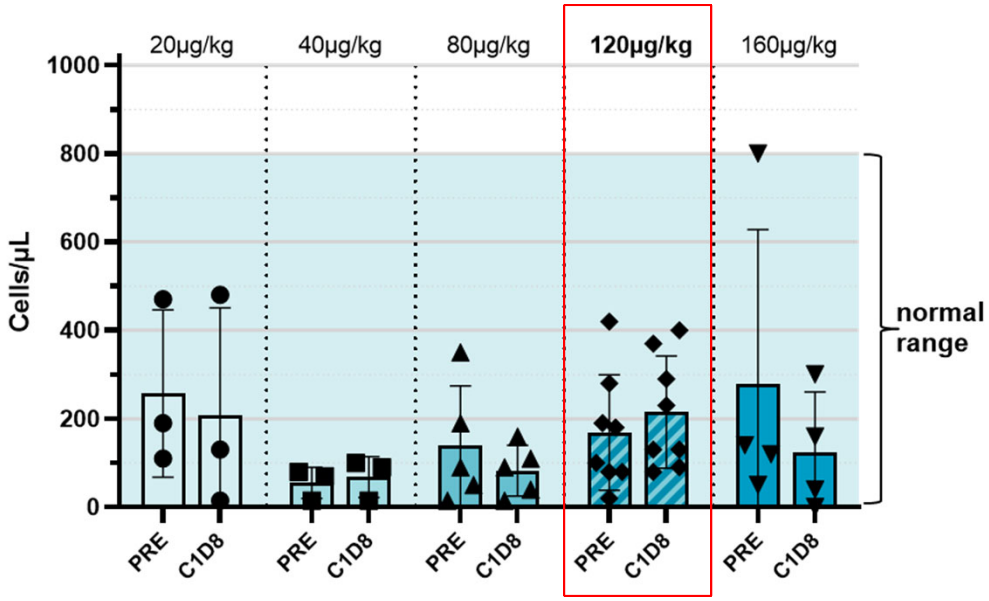


Lymphocytes (cells/mL)	20 µg/kg (n=3)	40 µg/kg (n=4)	80 µg/kg (n=5)	120 µg/kg (n=8)
median pre-dose	1050	770	1330	1400
median 7 days post dose	**1250**	**1745**	**2745**	**4740**

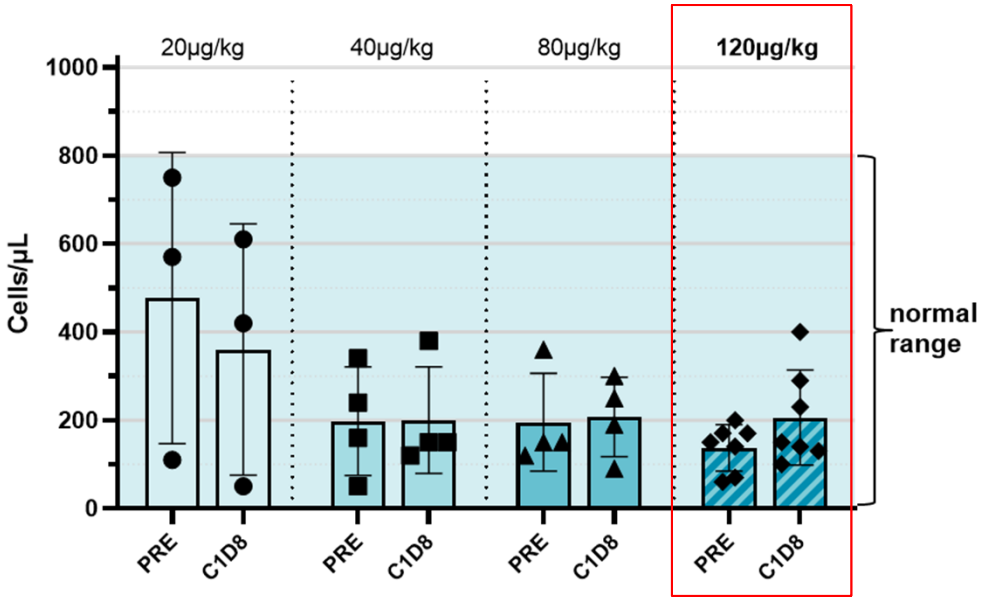
Each dot represents a single patient. The bar indicates the mean, and error bars indicate the standard deviation from the mean.
C1D8, cycle 1 day 8; pembro, pembrolizumab; PRE, pretreatment.

Lack of Eosinophil Expansion at Any Dose Level

Absolute Eosinophil Counts: TransCon IL-2 β/γ Monotherapy

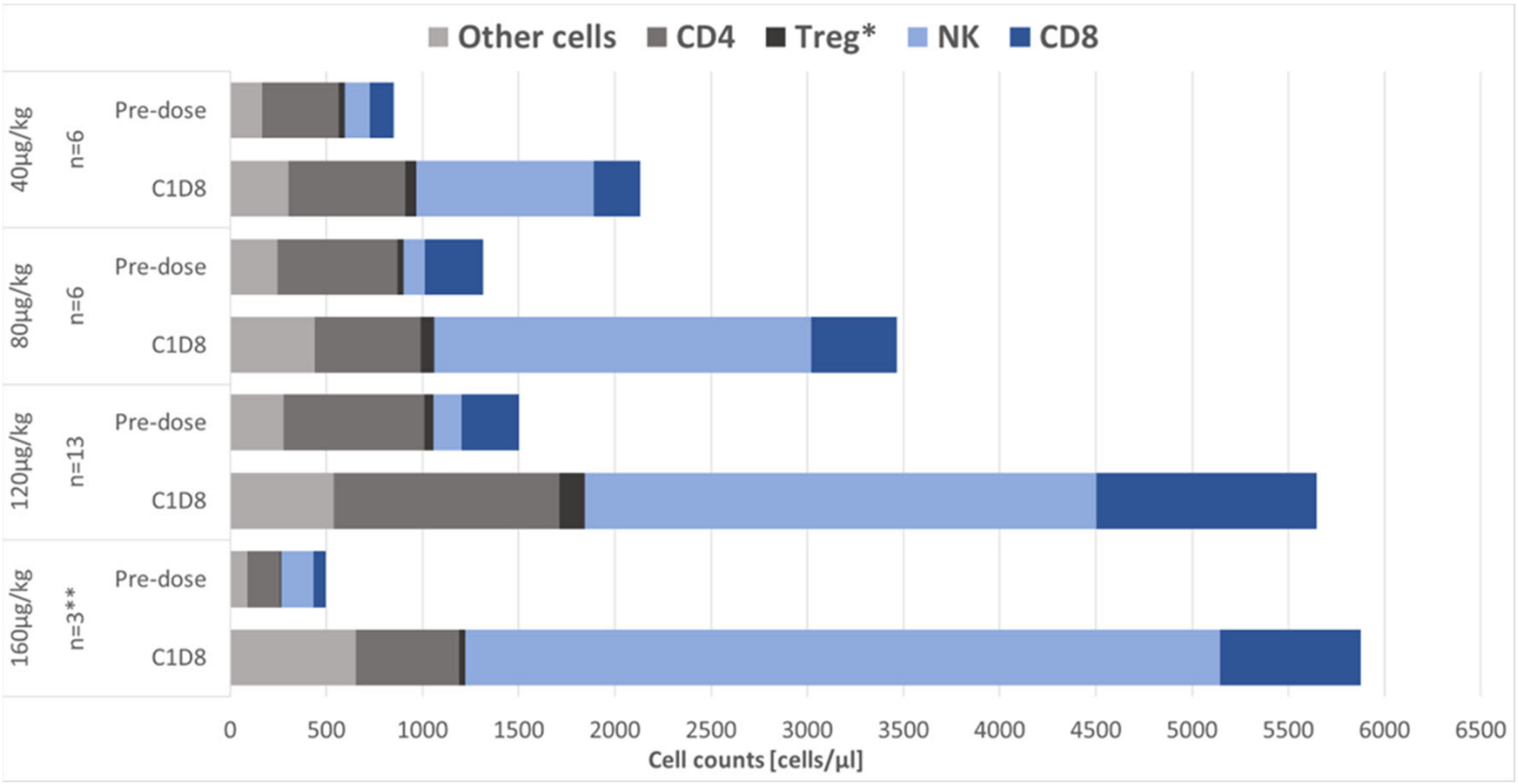


Absolute Eosinophil Counts: TransCon IL-2 β/γ + Pembro



Each dot represents a single patient. The bar indicates the mean, and error bars indicate the standard deviation from the mean.
C1D8, cycle 1 day 8; pembro, pembrolizumab; PRE, pretreatment.

Lymphocyte Composition Switches to Majority of Cytotoxic Lymphocytes 1 Week After Treatment

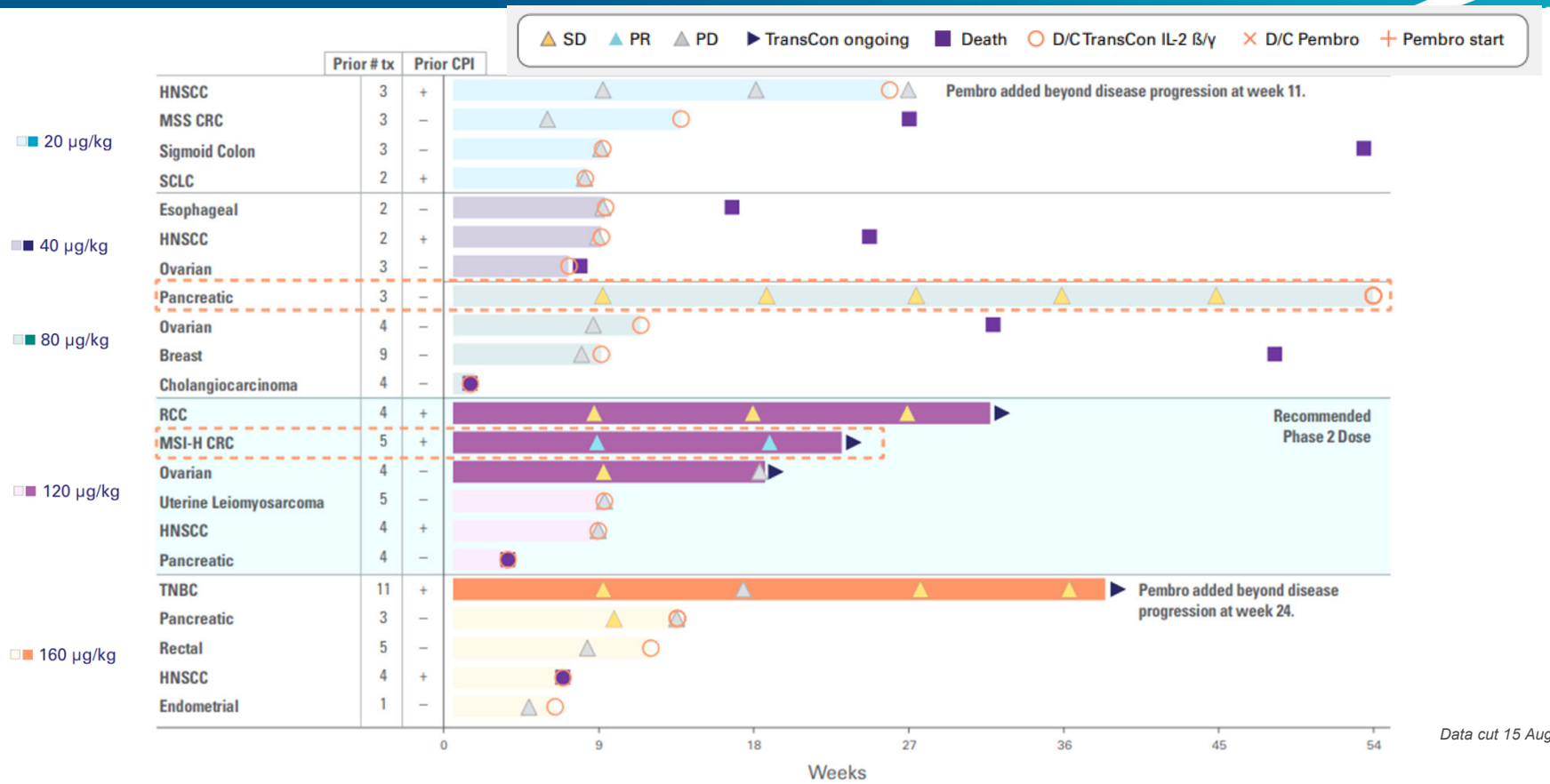


Similar lymphocyte compositions were observed in monotherapy and combination cohorts
Average cell count per dose-level - calculated from absolute lymphocyte count and flow cytometry data
*Cell count based on all available data. **Only monotherapy treated patients
C1D8: Cycle 1 Day 8; CD4: $CD4^+$ T Cells; CD8: $CD8^+$ T Cells; NK: Natural Killer Cells; T_{reg}: Regulatory T Cells

Preliminary Anti-Tumor Efficacy

- As of 15 Aug 2023, clinical benefit observed with monotherapy and combination in heavily pre-treated patients
  - Confirmed partial response in a colorectal cancer (CRC) patient who progressed on prior anti-PD-1 (Part 1, monotherapy at 120 µg/kg)
  - Confirmed partial response in a small cell lung cancer (SCLC) patient in Part 2, combination therapy at 80 µg/kg who progressed on prior anti-PD-L1
  - Clinical benefit in a pancreatic cancer patient with durable stable disease >45 weeks (Part 1, monotherapy at 80 µg/kg)
- As of 02 Oct 2023, 1 unconfirmed complete response (CR) in a patient with SCLC who progressed on prior anti-PD-1 in Part 2, combination therapy at 120 µg/kg (Figure 13)
- TransCon IL-2 β/γ demonstrates clinical activity as monotherapy or in combination with pembrolizumab across tumor types

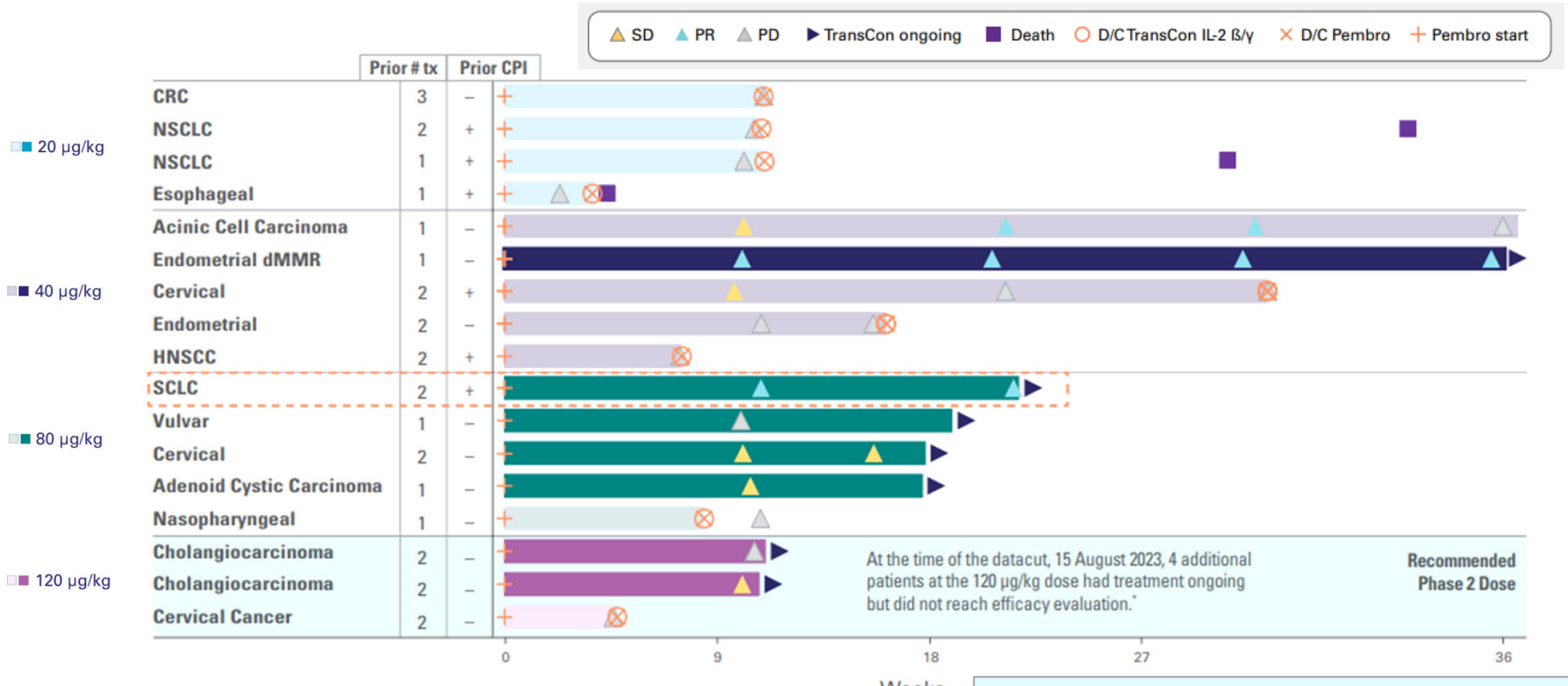
Part 1 Patient Status by Investigator Assessment Per RECIST v1.1



Data cut 15 Aug 2023

tx, number of lines of systemic treatment; CPI, checkpoint inhibitor; CRC, colorectal cancer; D/C, discontinuation; HNSCC, head and neck squamous cell cancer; MSI-h, microsatellite instability high; MSS, microsatellite stable; PD, progressive disease; PR, partial response; RCC, renal cell carcinoma; SCLC, small cell lung cancer; SD, stable disease;TNBC, triple-negative breast cancer.

Part 2 Patient Status by Investigator Assessment Per RECIST v1.1



Post data cut, as of 02 Oct 2023: 2 patients discontinued due to PD; 1 patient discontinued due to AE (SD at first assessment); 1 patient (SCLC post-anti-PD-1) CR at first assessment, treatment ongoing

 # tx, number of lines of systemic treatment; CPI, checkpoint inhibitor; CRC, colorectal cancer; dMMR, deficient mismatch repair; HNSCC, head and neck squamous cell cancer; NSCLC, non small cell lung cancer; SCLC, small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; CR, complete response; AE, adverse event

Data cut 15 Aug 2023

Percent Change from Baseline in Target Lesions by Dose Level

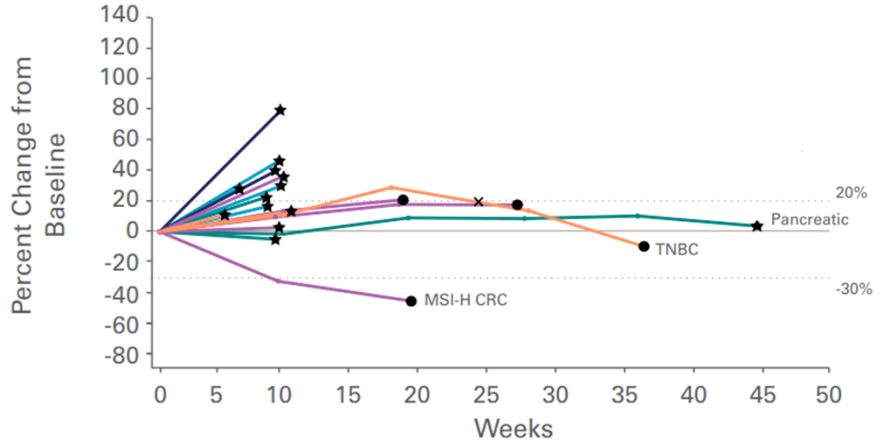
● TransCon IL-2 ß/γ ongoing
★ D/C TransCon IL-2 ß/γ
× Pembro beyond PD

Dose Level

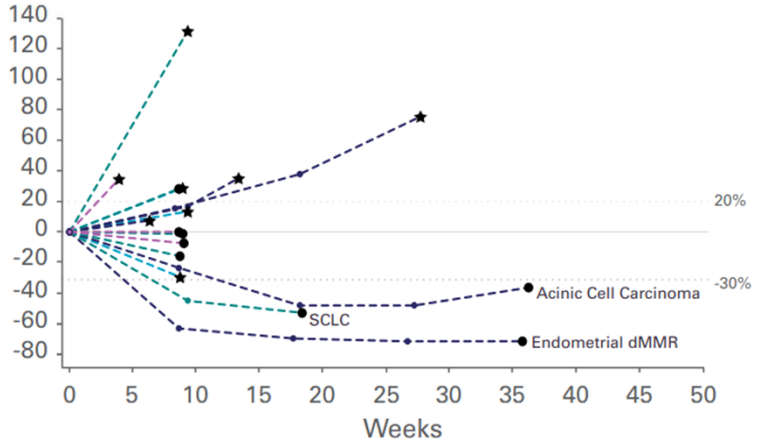
Monotherapy:
- TransCon IL-2 ß/γ 20 µg/kg
- TransCon IL-2 ß/γ 40 µg/kg
- TransCon IL-2 ß/γ 80 µg/kg
- TransCon IL-2 ß/γ 120 µg/kg
- TransCon IL-2 ß/γ 160 µg/kg

Combination Therapy:
- TransCon IL-2 ß/γ 20 µg/kg + pembro
- TransCon IL-2 ß/γ 40 µg/kg + pembro
- TransCon IL-2 ß/γ 80 µg/kg + pembro
- TransCon IL-2 ß/γ 120 µg/kg + pembro

Monotherapy



Combination Therapy



IL Trial Believe Response by Investigator Assessment per RECIST v1.1. Data cut 15 Aug 2023

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Case 1: Part 1, Monotherapy, Heavily Pre-treated Metastatic MSI-H Colorectal Cancer with Partial Response Post Anti-PD-1 Progression

Patient with metastatic colorectal cancer (CRC):

- Tumor genetics: Microsatellite Instability High (MSIh); BRAF V600E
- Prior 5 lines of systemic treatments, including nivolumab, all with Best Overall Response of Stable Disease (SD)
- Started on TransCon IL-2 β/γ monotherapy 120 μg/kg every 3 weeks since February 2023, now ongoing after 9 cycles
- Treatment related adverse events: Grade 2 fever, Grade 2 myalgia, Grade 1 rash, Grade 1 pruritis

Tumor assessment at Week 9 and 18: Partial Response (PR):

- Target lesions: peritoneal deposit next to spleen and omental soft tissue nodule
- Non-target lesions: omentum/peritoneum

Visit	Sum of Diameters in mm (% change from baseline)	Target Lesion Response	Non-target Response	New Lesion	RECIST v1.1 Overall Response
Baseline	46				
Week 9	31 (-33%)	PR	Non-CR/Non-PD	No	PR
Week 18	25 (-45.6%)	PR	Non-CR/Non-PD	No	PR

Partial Response on monotherapy TransCon IL-2 β/γ

BOR=best overall response; SD=stable disease; PR=partial response

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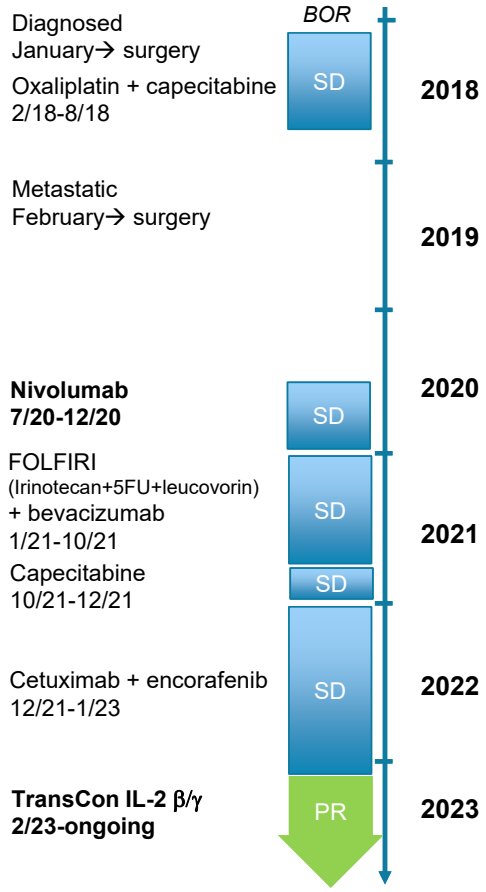
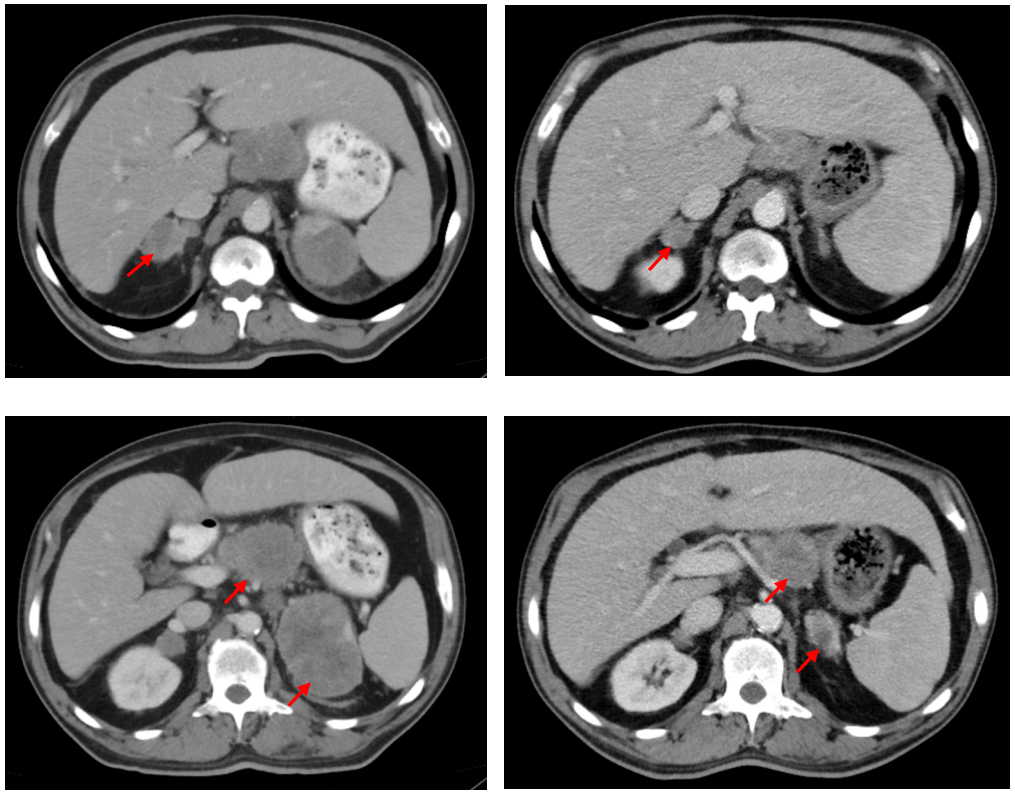


Case 2: Part 2, Combination, Heavily Pre-treated Metastatic Small Cell Lung Cancer with Partial Response Post Anti-PD-L1 Progression

Baseline → Week 18

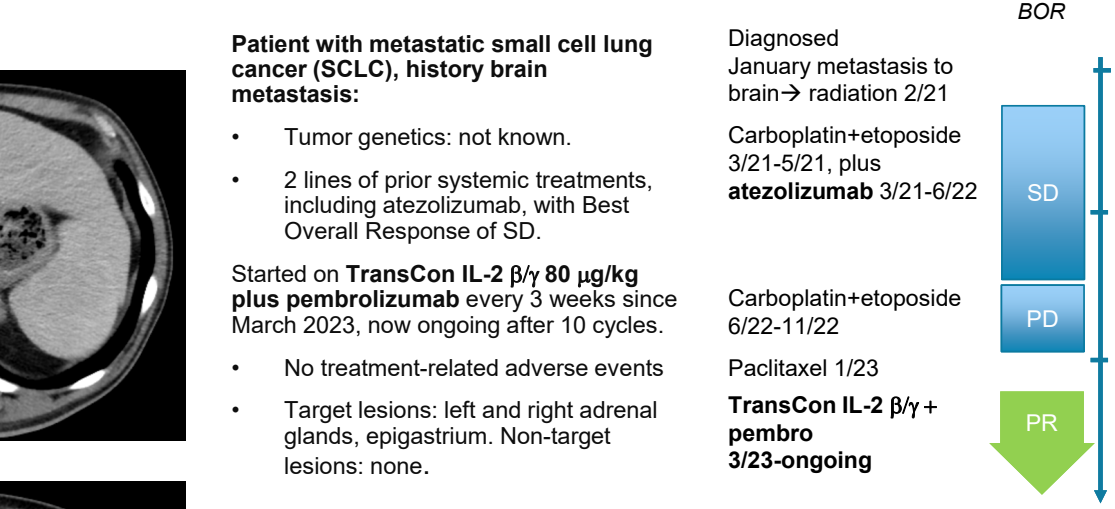


Patient with metastatic small cell lung cancer (SCLC), history brain metastasis:

- Tumor genetics: not known.
- 2 lines of prior systemic treatments, including atezolizumab, with Best Overall Response of SD.

Started on **TransCon IL-2 β/γ 80 μg/kg plus pembrolizumab** every 3 weeks since March 2023, now ongoing after 10 cycles.

- No treatment-related adverse events
- Target lesions: left and right adrenal glands, epigastrium. Non-target lesions: none.



Visit	Sum of Diameters in mm (% change from baseline)	Target Lesion Response	Non-target Response	New Lesion	RECIST v1.1 Overall Response
Baseline	217				
Week 9	119 (-45.1%)	PR	-	No	PR
Week 18	102 (-53%)	PR	-	No	PR
Week 27	99 (-54.3%)	PR	-	No	PR

Partial Response post anti-PD-L1 progression

Data cut 02 Oct 2023

BOR, best overall response; PD, progression disease; PR, partial response; SD, stable disease; SLD, sum of the longest diameter.

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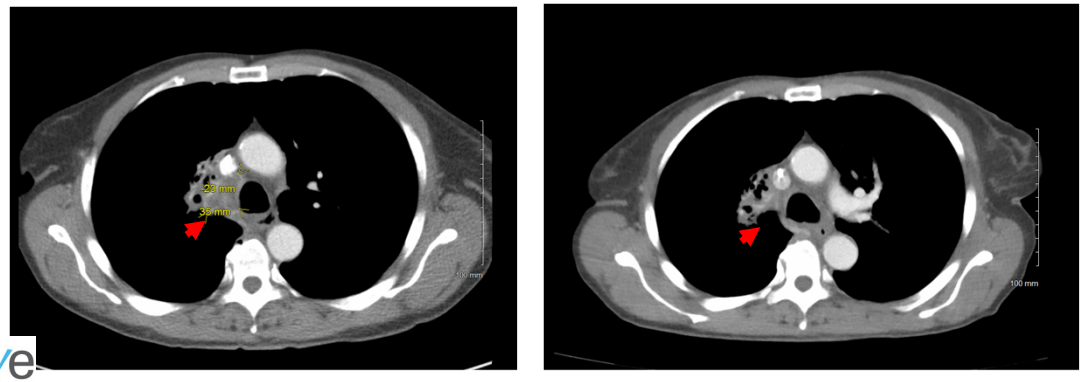
Case 3: Part 2, Combination, Metastatic Small Cell Lung Cancer with Complete Response post anti-PD-1 progression

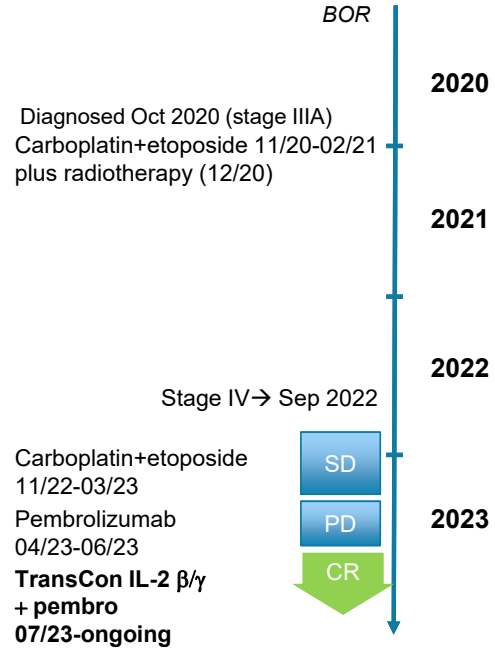
Patient with metastatic small cell lung cancer (SCLC):

- Tumor genetics: not known.
- 2 lines of prior metastatic systemic treatments, including pembrolizumab, with PD.
- Started on **TransCon IL-2 β/γ 120 μg/kg plus pembrolizumab** every 3 weeks since 13 July 2023, now ongoing after **4 cycles.**
- **No treatment-related adverse events**
- Target lesion: **Paratracheal mass.** Non-target lesions: none.

Visit	Sum of Diameters in mm (% change from baseline)	Target Lesion Response	Non-target Response	New Lesion	Overall Response
Baseline	35				
Week 9	0 (-100%)	CR	-	No	CR

Baseline → Week 9





Complete Response post anti-PD-1 progression

BOR, best overall response; PD, progression disease; CR, complete response; SD, stable disease; SLD, sum of the longest diameter.

Data cut 02 Oct 2023

Conclusions

- In the ongoing IL-Believe trial TransCon IL-2 β/γ has been well-tolerated as a monotherapy or in combination with pembrolizumab with RP2D determined at 120 µg/kg
- PK data demonstrated a long half-life of TransCon IL-2 β/γ of ~37 hours
- PD data demonstrated expansion of lymphocytes, leading to a predominantly cytotoxic lymphocyte composition, while there was no meaningful increase of eosinophils or T_{regs}
- Anti-tumor clinical responses have been observed with TransCon IL-2 β/γ monotherapy (CRC with confirmed partial response (PR)) or in combination with pembro (SCLC, 1 with confirmed PR and 1 ongoing with unconfirmed CR) in heavily pre-treated patients who previously progressed on checkpoint inhibitors
- Study continues to enroll (ClinicalTrials.gov NCT05081609)

Thank you

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