Ascendis Pharma A/S

Oncology Program Update

May 31, 2023

Cautionary Note on Forward-Looking Statements

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.

Any forward-looking statement made by us in this presentation speaks only as of the date of this presentation and represents our estimates and assumptions only as of the date of this presentation. Except as required by law, we assume no obligation to update these statements publicly, whether as a result of new information, future events, changed circumstances or otherwise after the date of this presentation.

This presentation concerns product candidates that are or have been under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration, European Medicines Agency or other foreign regulatory authorities. These product candidates are currently limited by U.S. Federal law to investigational use, and no representations are made as to their safety or effectiveness for the purposes for which they are being investigated.

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Oncology R&D Day Agenda

10:00 a.m.

Welcome & Agenda Overview
Scott T. Smith, EVP, CFO

10:05-10:20 a.m.

Vision 3x3
Jan Møller Mikkelsen, President & CEO

10:20-10:35 a.m.

TransCon™ Platform & Product Innovation
Kennett Sprogøe, Ph.D.
EVP, Head of Innovation and Research

10:35-11:10 a.m.

Clinical Development Strategy & Clinical Updates
Stina Singel, M.D., Ph.D.
EVP, Head of Clinical Development, Oncology

11:10-11:30 a.m.

Investigator Perspectives
Diwakar Davar, M.D.
Associate Professor; Clinical Director of Melanoma & Skin Cancer Program, University of Pittsburgh Medical Center (UPMC), Hillman Cancer Center

11:30-12:00 p.m.

Closing Remarks
Jan Møller Mikkelsen, President & CEO

Q&A
Moderated by Scott T. Smith, EVP, CFO

Vision 3x3
Our Vision for Oncology

Jan Mikkelsen
President & Chief Executive Officer

Vision 3x3: Building a Leading Global Biopharma Company

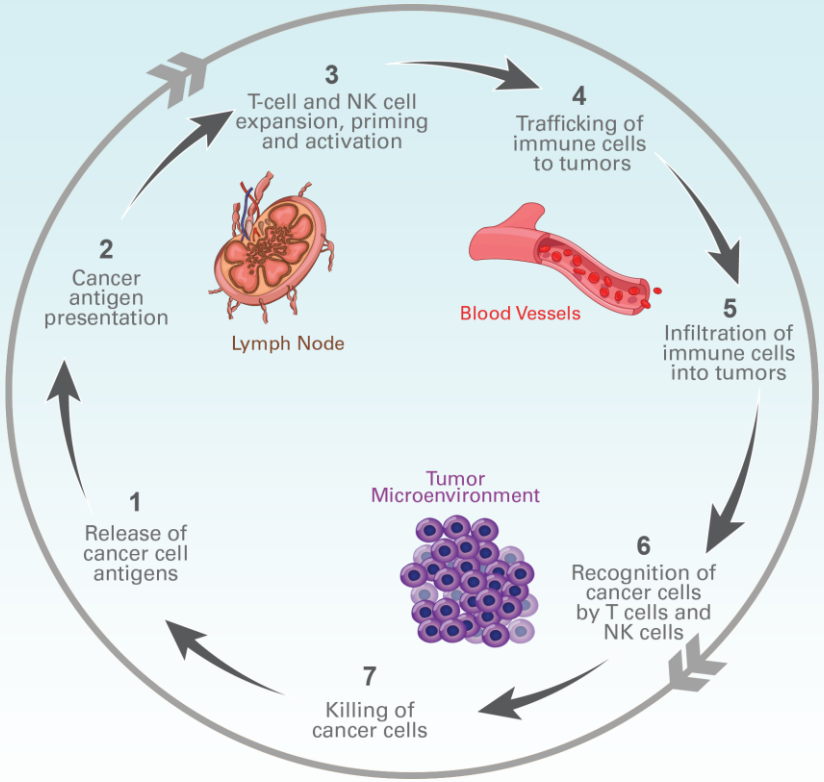
Our goal is to achieve sustainable growth through multiple approaches

- **Obtain regulatory approval for three independent Endocrinology Rare Disease products**
  - TransCon hGH for pediatric growth hormone deficiency
  - TransCon PTH for adult hypoparathyroidism
  - TransCon CNP for achondroplasia
- **Grow Endocrinology Rare Disease pipeline through**
  - Global clinical reach
  - Pursuing 9 total indications, label optimization, and life cycle management
  - New endocrinology products
- **Establish global commercial presence for our Endocrinology Rare Disease area**
  - Build integrated commercial organization in North America and select European countries
  - Establish global commercial presence through partners with local expertise and infrastructure
- **Advance a high-value oncology pipeline with one IND or similar filing each year**
- **Create a third independent therapeutic area with a diversified pipeline**

Ascendis Pharma's 2020 - 2025 strategic roadmap

Why Oncology?

- Very large unmet medical need
- Large number of clinically validated pathways which are limited by toxicity, efficacy, and ease of administration
- Suitable for use with the TransCon Technology platform
  - Systemic delivery
  - Localized delivery
- Potential to address all the aspect of the cancer immunity cycle



Opportunity to expand pipeline to impact multiple aspects of anti-tumor response

Interleukin 2 Overview

First immunologic compound in cancer

- FDA approved for the treatment of metastatic renal cell carcinoma (1992)
- FDA approved for the treatment for metastatic melanoma (1998)

Clinical response data - Metastatic renal cell carcinoma

	Number of Responding Patients (response rate)	Median Response Duration in Months (range)
CR's	17 (7%)	80+* (7 to 131+)
PR's	20 (8%)	20 (3 to 126+)
PR's + CR's	37 (15%)	54 (3 to 131+)

Clinical response data - Metastatic melanoma

	Number of Responding Patients (response rate)	Median Response Duration in Months (range)
CR's	17 (6%)	59+* (3 to 122+)
PR's	26 (10%)	6 (1 to 111+)
PR's + CR's	43 (16%)	9 (1 to 122+)

Proleukin (aldesleukin) product label
(+) sign means ongoing
* Median duration not yet observed; a conservative value is presented which represents the minimum median duration of response.

Interleukin shown to be effective in approximately 15% of patients

TransCon™ Technology Platform & Product Innovation in Oncology

Kennett Sprogøe, Ph.D.
EVP, Head of Innovation and Research

TransCon: An Innovative Technology Platform

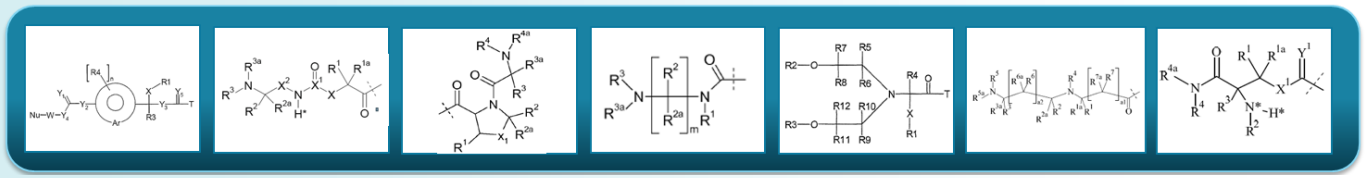
- TransCon technologies combine the benefits of prodrug and predictable release technologies.
  - TransCon soluble prodrug technology validated within endocrinology with a high success rate in multiple clinical programs; SKYTROFA® approved in the EU and US.
  - TransCon hydrogel technology applied as a long-acting intratumoral (IT) delivery platform of small molecules, peptides, proteins, antibody fragments and antibodies.
- TransCon IL-2 β/γ is using same soluble prodrug technology as SKYTROFA, enabling sustained released of potent non-alpha IL-2.
- TransCon TLR7/8 Agonist is using our hydrogel technology for sustained intratumoral immune activation, with minimal systemic exposure.

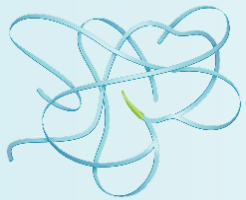
TransCon platform is uniquely suited for amplified and durable immune activation, with the aim for addressing significant unmet medical need

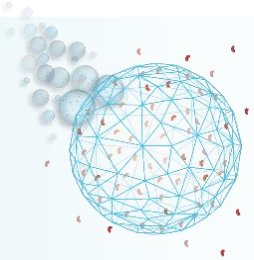
*Trans*ient *Con*jugation: A Powerful, Flexible Platform

TransCon Platform: 3 components

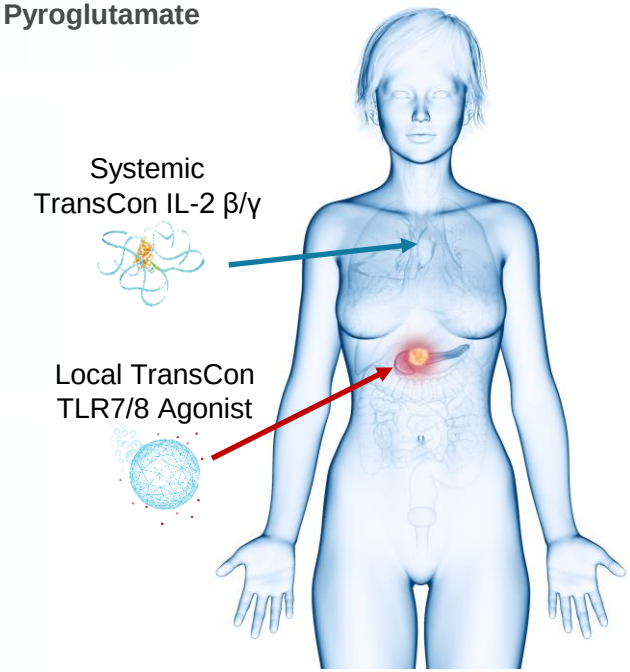
- TransCon Linker
- TransCon Carrier
- Parent Drug




Soluble Carriers

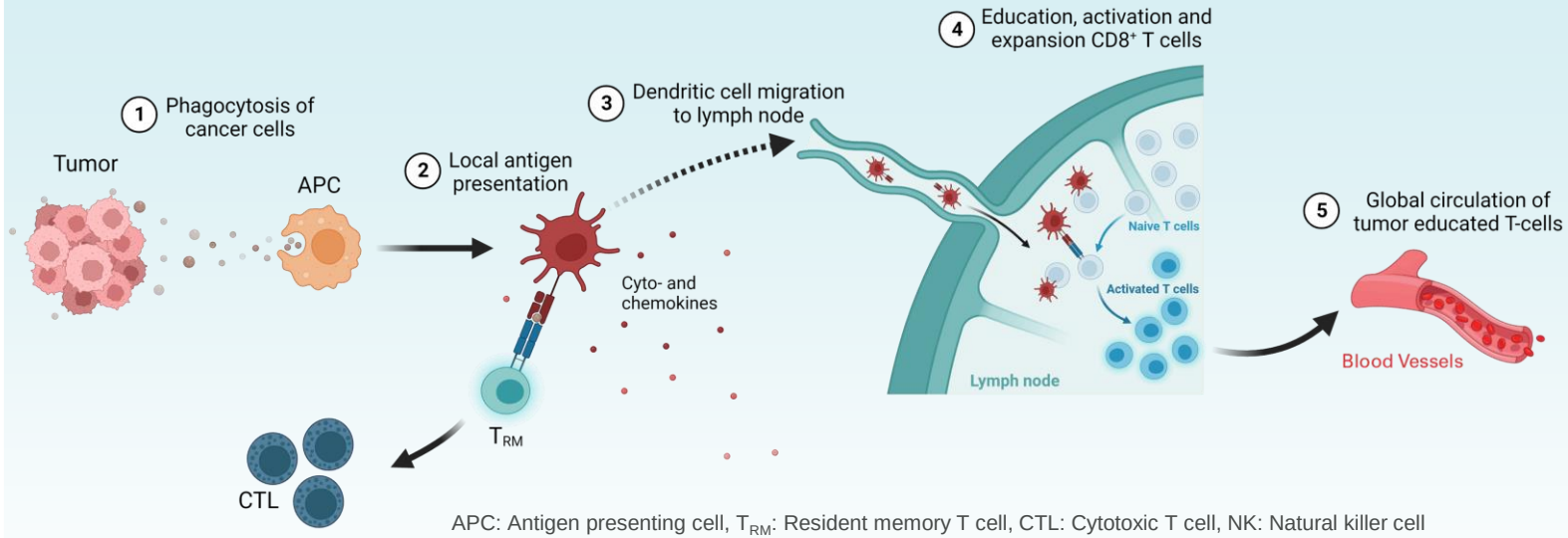

Insoluble Carriers


Antibodies, Antibody Fragments, Proteins, Peptides and Small Molecules



Leveraging the breath of TransCon platform to design pipeline of immuno-oncology drugs

Stimulating Local Immunity to Achieve Systemic Effect



APC: Antigen presenting cell, T_{RM}: Resident memory T cell, CTL: Cytotoxic T cell, NK: Natural killer cell

Innate immune stimulator

TransCon TLR7/8 Agonist for long-acting IT delivery

- Turns the tumor hot
- Enhances education of T cells
- Recruits systemic cytotoxic immune cells

Adaptive immune stimulator

TransCon IL-2 β/γ for long-acting systemic delivery

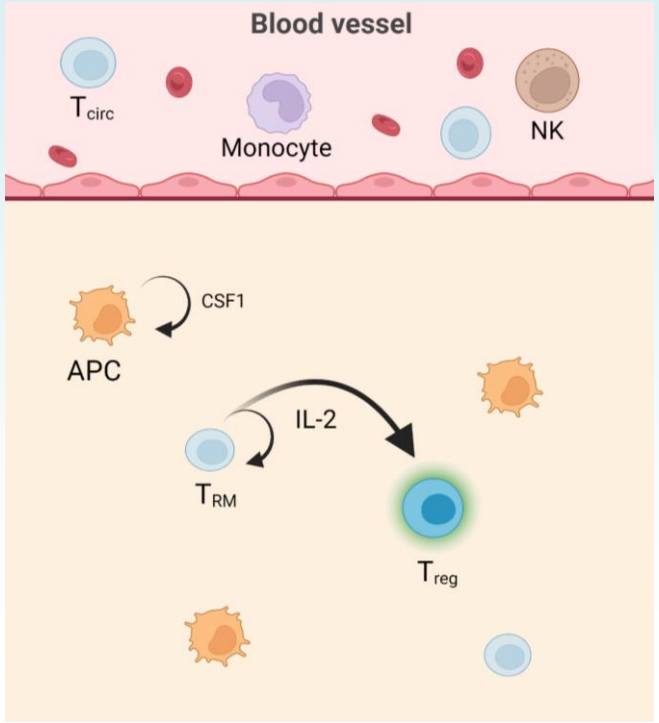
- Expands & activates $CD8^+$ T and NK cell population
- Activates tumor resident effector cells locally

TransCon IL-2 β/γ and TransCon TLR7/8 Agonist have been designed mechanistically for monotherapy and synergistic combination effects

The Immune System in Normal Compared to Inflamed Tissue

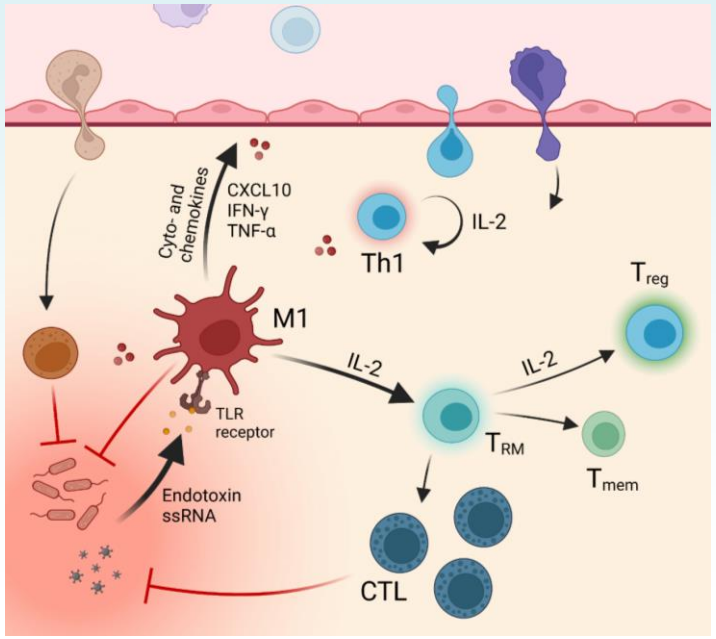
Normal tissue

- Tissue resident immune cells survey all organs and act as first responders in response to threats



Inflamed tissue

- Local chemokines attract effector cells from blood and surrounding tissue
- Local cytokines such as IL-2 proliferate, activate and potentiate the immune response

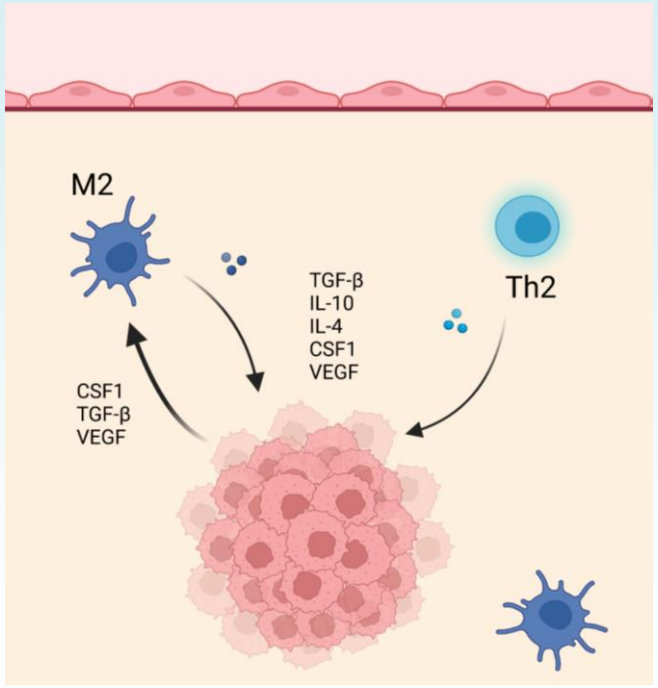


T_{circ}: Circulating T cells, NK: Natural killer cells, APC: Antigen presenting cell, T_{RM}: Tissue resident T cell (effector & memory), CTL: Cytotoxic T cell ($CD8^+$), T_{mem}: Memory T cell ($CD4^+$), Th1: T helper 1 cell, M1: M1 macrophage

The Immune System in Cold versus Hot Tumors

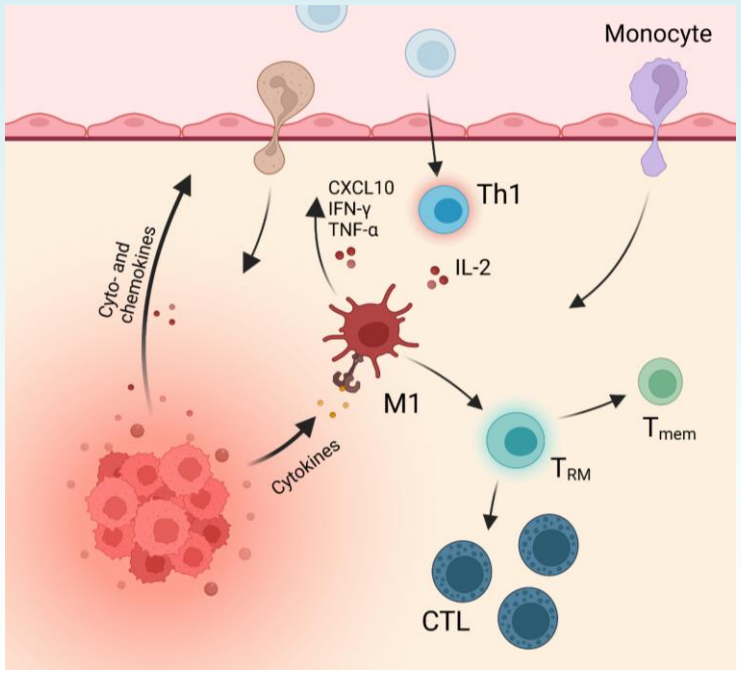
Cold tumors

- In cold tumors, there is no inflammation and no recruitment of effector cells



Hot tumor

- In hot tumors, the tissue resident immune cells fight the cancer and may recruit effector cells from circulation



Innate activators like TLR7/8 Agonist can turn a cold tumor hot

T_{circ}: Circulating T cells, NK: Natural killer cells, APC: Antigen presenting cell, T_{RM}: Tissue resident T cell (effector & memory), CTL: Cytotoxic T cell ($CD8^+$), T_{mem}: Memory T cell ($CD4^+$), Th1 & Th2: T helper 1 or 2 cell, M1 & M2: M1- or M2-like macrophage

Optimal Product Design Parameters

Innate immune system

Ideal TLR agonist

Design

- Sustained high local concentration
- Potent pro-inflammatory TLR agonist

Pharmacology / PD

- Sustained inflammation in the tumor, with high cyto- and chemokine release
- Convenient dosing

Clinical

- Clinical activity in injected and non-injected tumor (abscopal)
- Well-tolerated systemic AE profile

Adaptive immune system

Ideal IL-2 agonist

Design

- Long systemic half-life with low Cmax
- IL-2 biased to β/γ with high potency and similar size to native IL-2

Pharmacology / PD

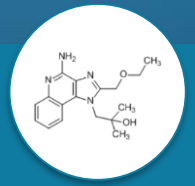
- Expansion of $CD8^+$ T and NK cells, with no expansion of EOS and T_{regs}
- Convenient dosing

Clinical

- Broad clinical activity
- Well-tolerated (no grade 3/4 CRS, VLS)
- Administered as outpatient

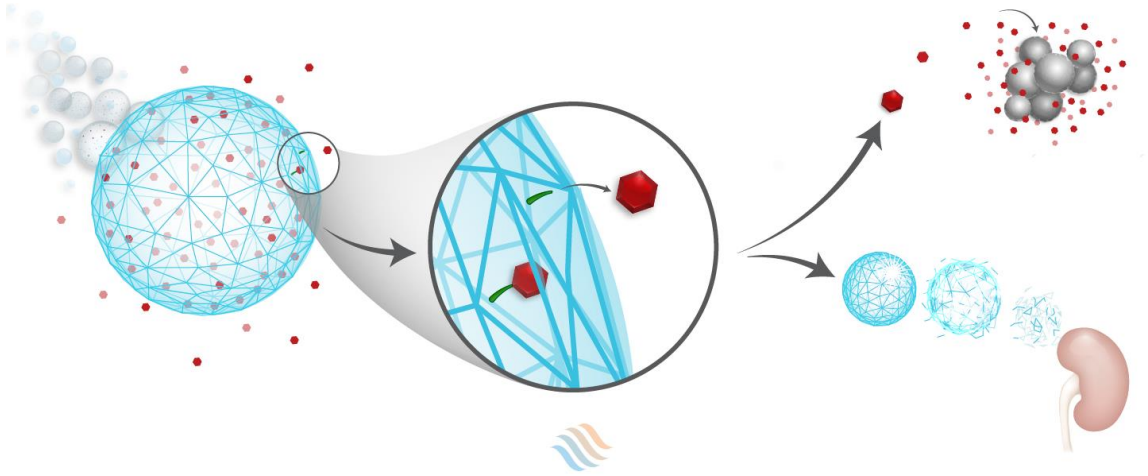
TLR: Toll-like receptor; Treg: regulatory T cells; EOS: eosinophils; ALC absolute lymphocytes count (blood); CRS: cytokine release syndrome; VLS: vascular leak syndrome

TransCon TLR7/8 Agonist: Using TransCon Hydrogel Technology for Targeted Intratumoral Exposure



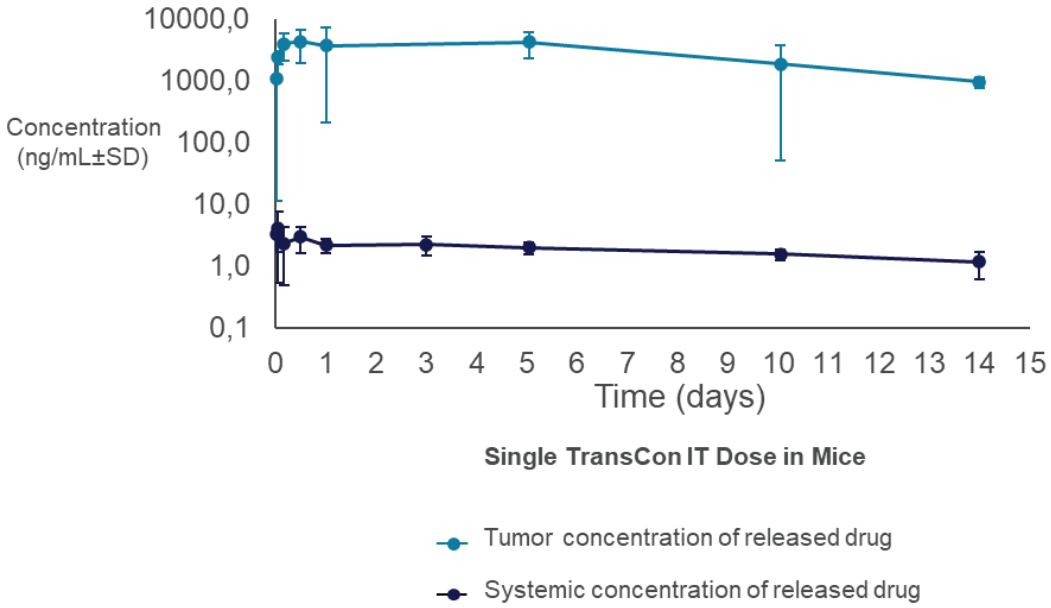
TransCon TLR7/8 Agonist

Sustained Local Intratumoral Release of Resiquimod



Local depot of drug loaded TransCon hydrogel carrier

pH and temperature dependent linker cleavage

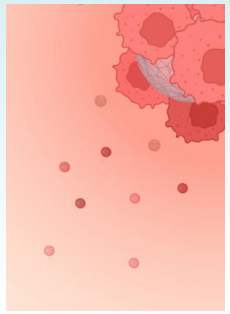


Using TransCon hydrogel enables high local concentration of resiquimod with low systemic exposure

TransCon TLR7/8 Agonist: Turning the Tumor Hot

- TransCon TLR7/8 Agonist is designed for high intratumoral exposure over several weeks with minimal systemic exposure and to turn the tumor hot using a potent TLR agonist[1]
- Local and abscopal effect expected via increased antigen presentation in tumor & draining lymph nodes[2]

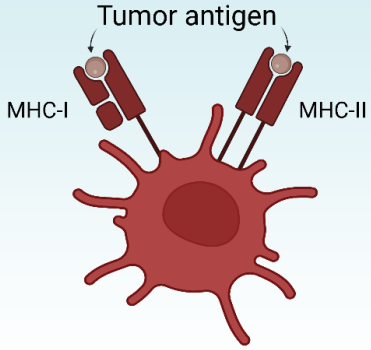
Increase intratumoral proinflammatory cytokines



Production of chemokines

CXCL-10 creates homing of T_{eff} and NK cells from tissue and blood.

Increase antigen presentation



TransCon TLR7/8 Agonist is designed to activate the antigen presenting cells locally and make tumors hot regardless of immune status

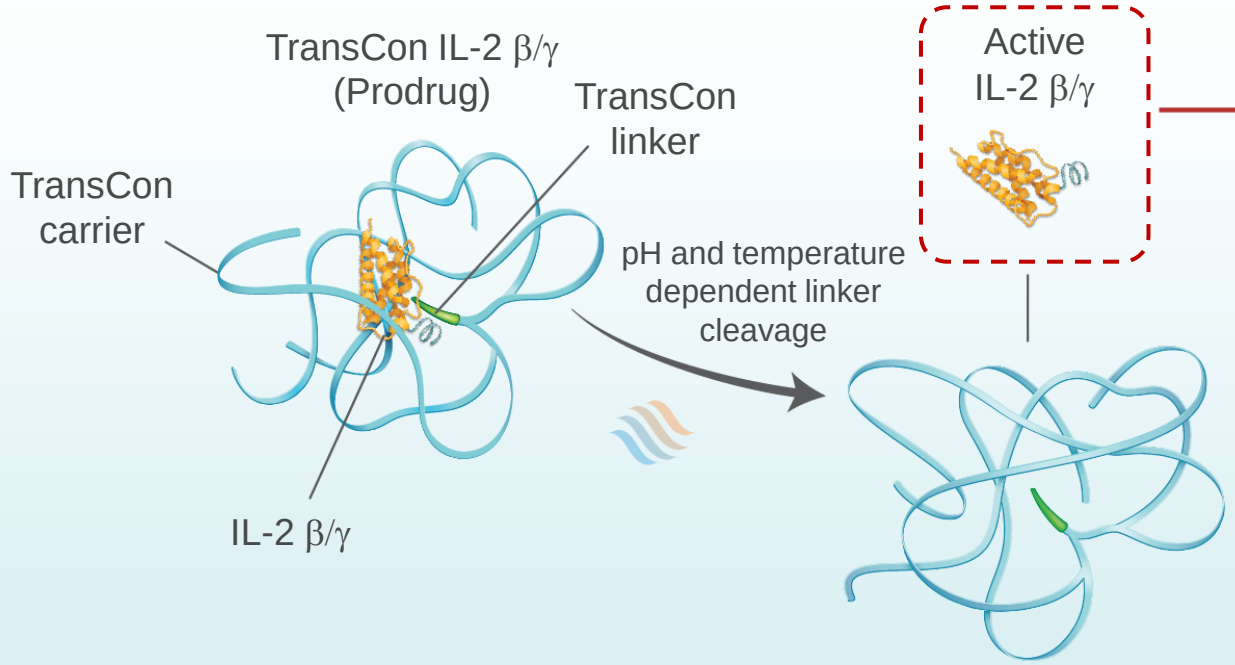
[1] *Cellular Immunology 243 (2006) 48–57* [2] *Cancer Cell International (2022) 22:286*

TransCon IL-2 β/γ: Sustained Release of Non-alpha IL-2 Using Validated Prodrug Technology

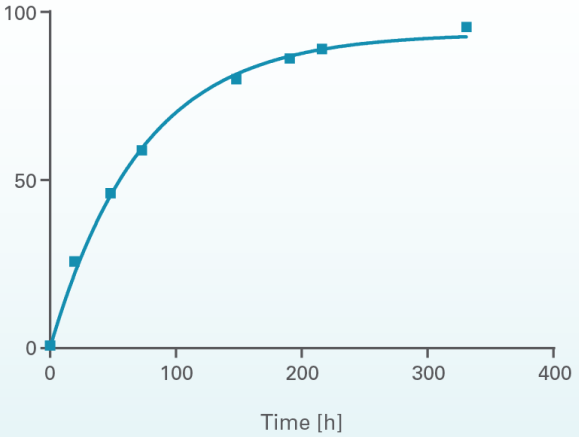
TransCon
IL-2 β/γ

TransCon IL-2 β/γ Best-in-Class Design

TransCon linker slowly releases IL-2 β/γ



TransCon IL-2 β/γ *in vitro* release kinetics



TransCon IL-2 β/γ is designed to provide sustained expansion of circulating $CD8^+$ T and NK cells. Released IL-2 β/γ can distribute to tumor tissue to active resident immune cells.

Rosen D, et al. AACR annual meeting. 2020; Poster 4507.

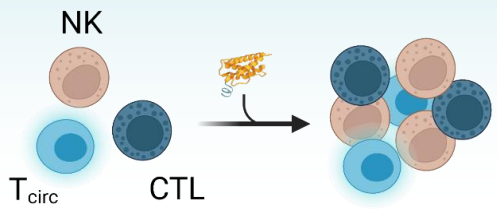
TransCon IL-2 β/γ: Built on 30 Years of Learnings

Designed for desired receptor binding, potency, and exposure

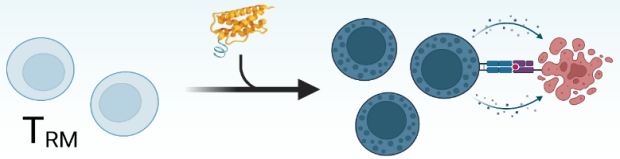
- β/γ bias obtained with small 5 kDa PEG, retaining native-like size and high potency to preferentially expand and activate cytotoxic T- and NK cells over T_{regs}
- Long half-life prodrug and low C_{max} widen therapeutic index to deliver tolerable and sustained expansion of effector cell

Variant	β/γ Bias	Potency reduction[1]	Size[2] (Radius)
IL-2	No	n/a	2 nm
IL-2 β/γ 5 kDa	Yes	~4-fold	3 nm
IL-2 β/γ 10 kDa	Yes	~6-fold	4 nm
IL-2 β/γ 30 kDa	Yes	~20-fold	6 nm

Selectively expand reservoir of cytotoxic T- and NK cells over T_{regs}



Locally activate tissue-resident cytotoxic T-cells

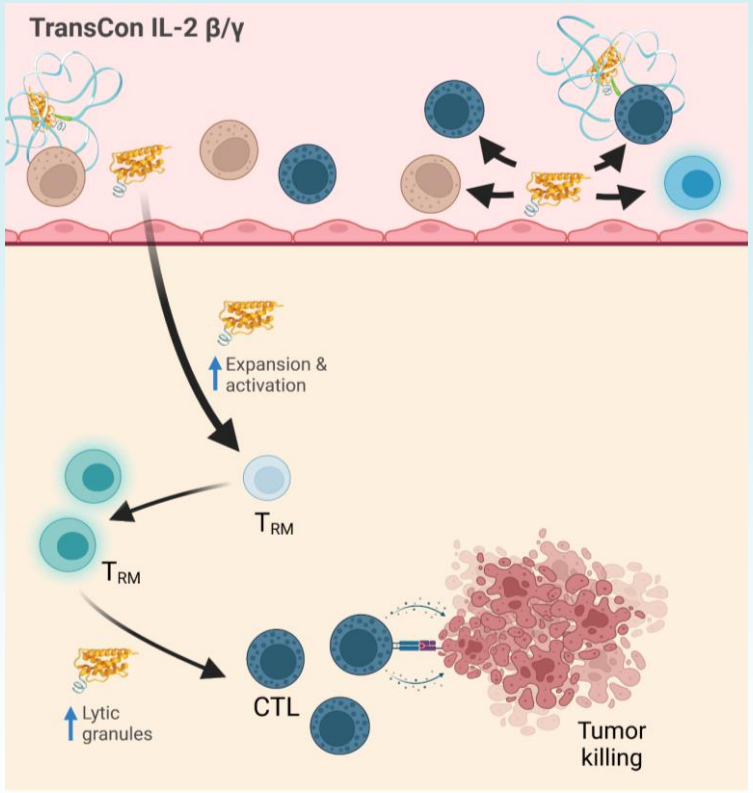


Low C_{max}, of released biased IL-2 β/γ molecule, retaining native-like size

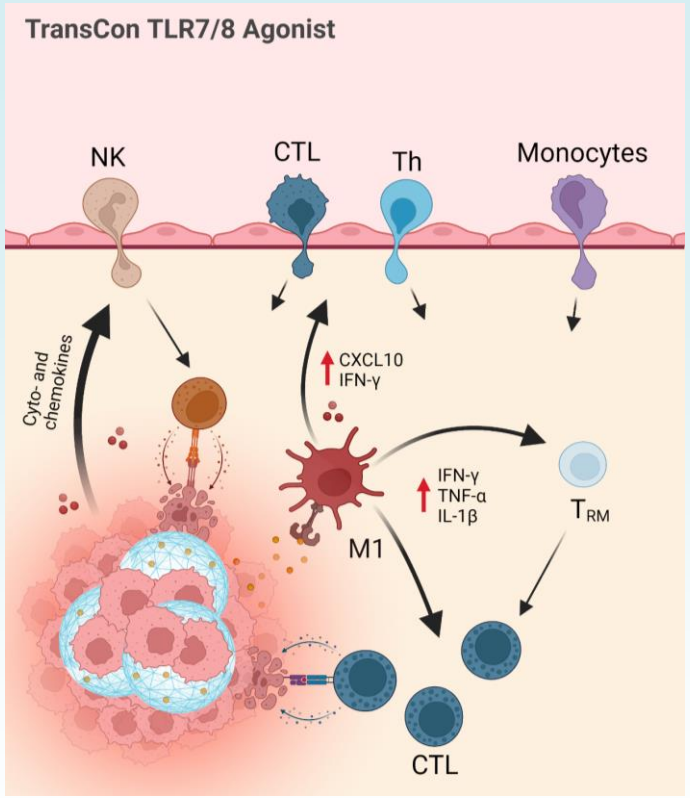
TransCon IL-2 β/γ is designed to enhance both local and systemic immune responses and synergize with hot tumor biology

[1]*Data on file*
[2]*Bioconjugate Chem.* 2004, 15, 6, 1304–1313

Two Products Designed for Monotherapy Effects and Synergistic Mode of Action



TransCon IL-2 β/γ designed to robustly expand and activate immune effector cells in tumor and circulation



TransCon TLR7/8 Agonist designed to increase tumor recognition for local and systemic tumor clearance

T_{circ}: Circulating T cells, NK: Natural killer cells, APC: Antigen presenting cell, T_{RM}: Tissue resident T cell (effector & memory), CTL: Cytotoxic T cell ($CD8^+$), T_{mem}: Memory T cell ($CD4^+$), Th1: T helper 1 cell, M1: M1 macrophage

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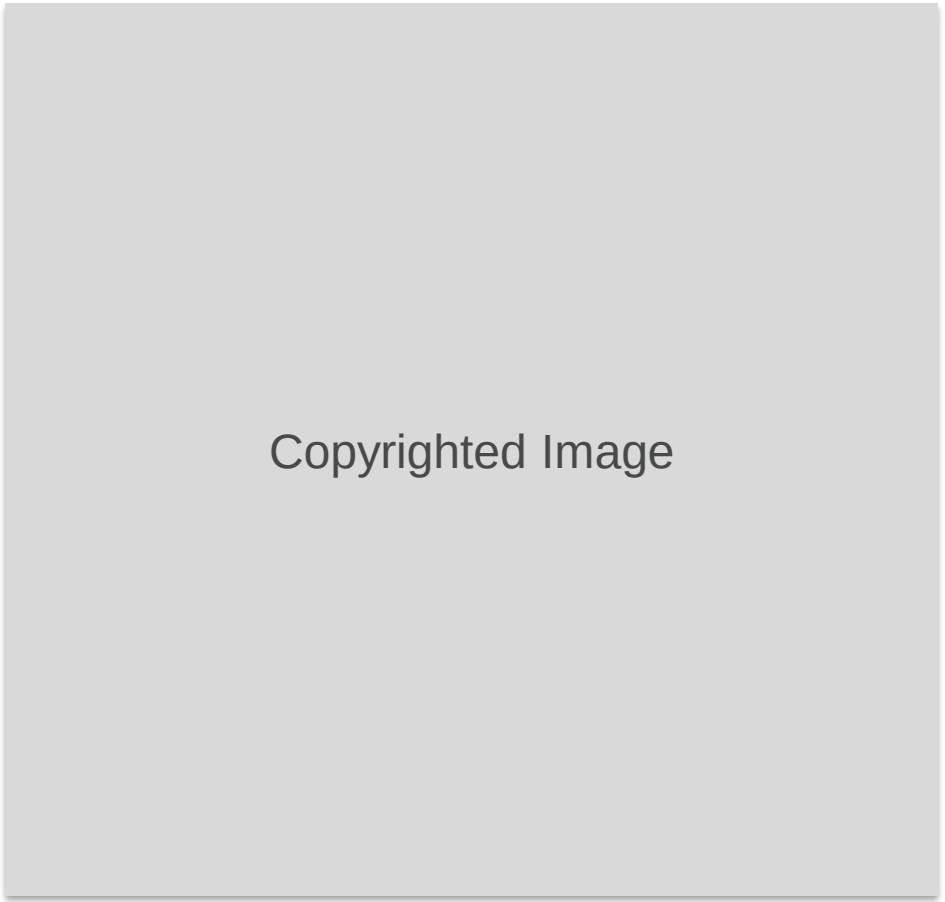
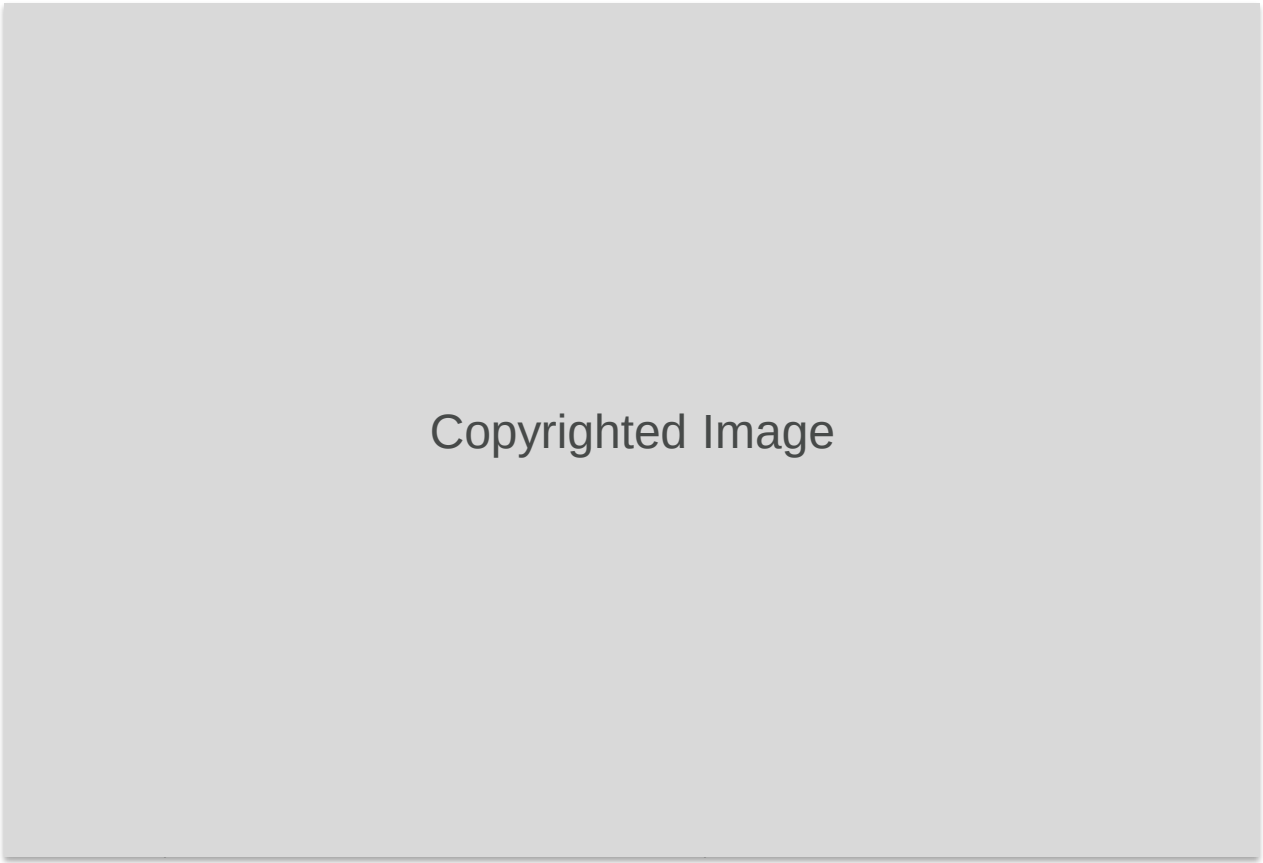
Clinical Development Strategy & Clinical Updates

Stina Singel, M.D., Ph.D.
EVP, Head of Clinical Development, Oncology

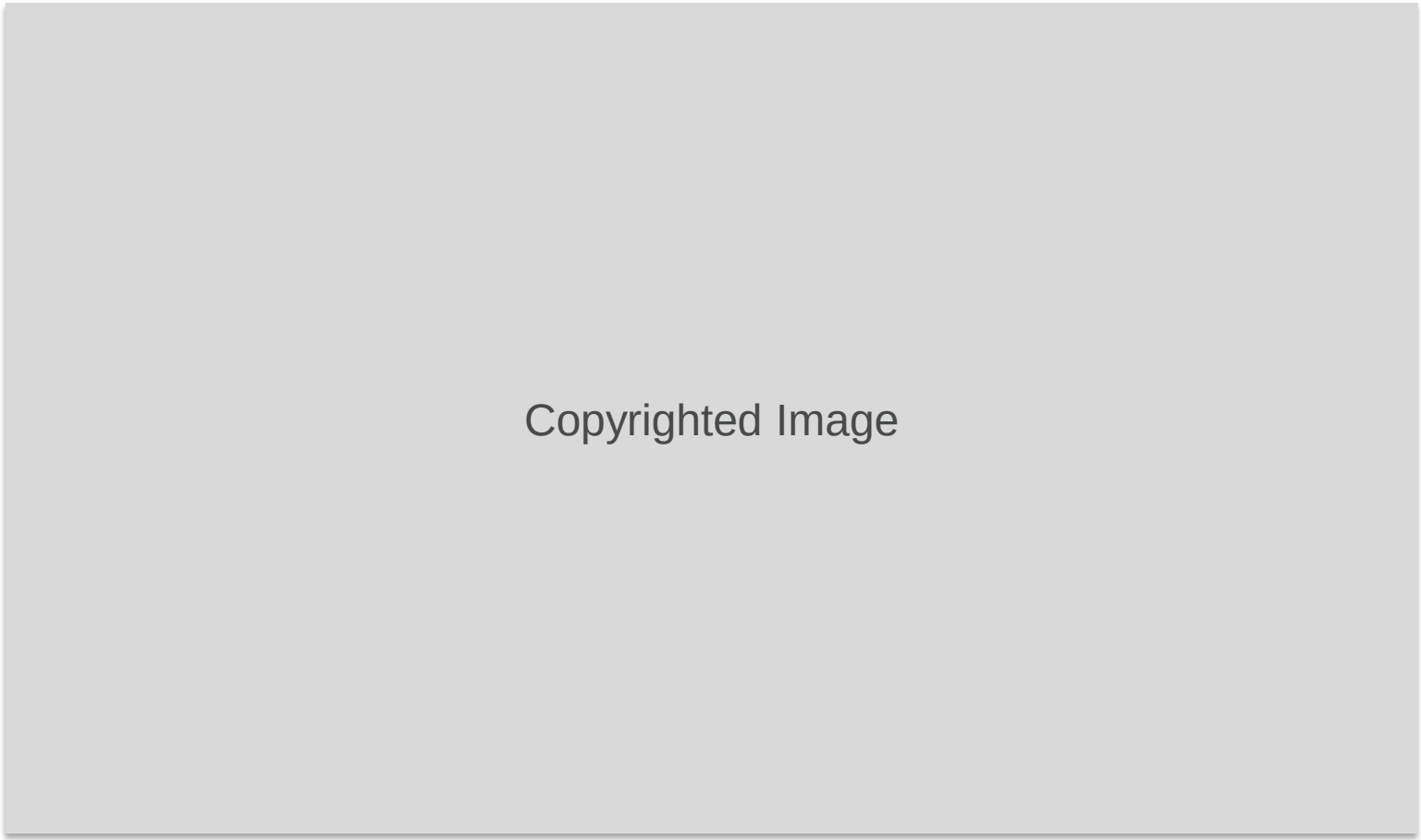
Removing the Immune Brakes Is Not Sufficient for Majority of Tumors





Primary and acquired resistance to immune checkpoint inhibitors limit the benefit from checkpoint inhibitors

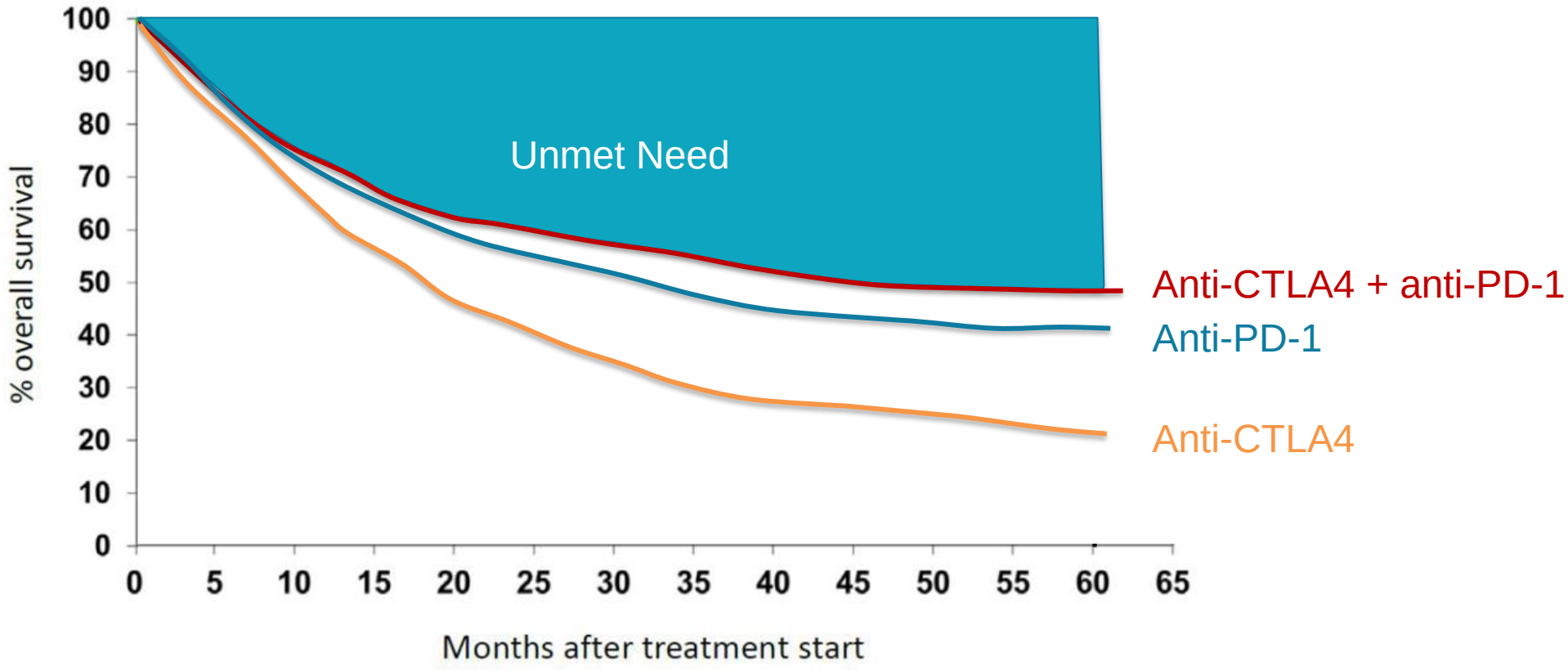
Melanoma is the First Solid Tumor to Demonstrate Benefit from Checkpoint Inhibitors



Checkpoint inhibitors and targeted therapies have made significant impact on melanoma survival

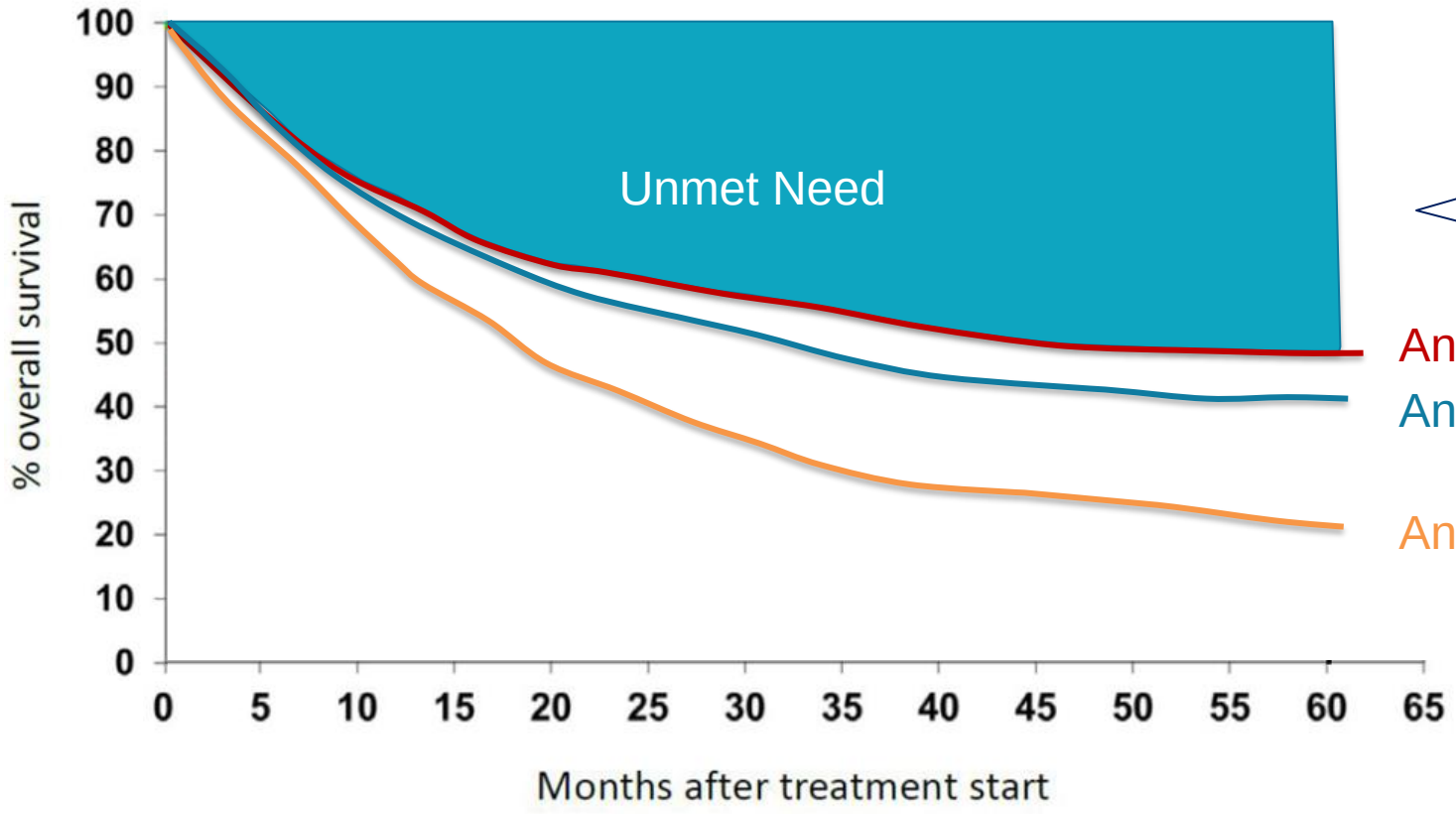
Reprinted from Eur J Cancer, Vol /edition number, Ugurel et al., Survival of patients with advanced metastatic melanoma: The impact of MAP kinase pathway inhibition and immune checkpoint inhibition - Update 2019, 2020; 130:126-138, with permission from Elsevier.

Many Patients Do Not Benefit Sufficiently from Checkpoint Inhibitors in Melanoma



Adapted from Ugurel et al. Eur J Cancer 2020; 130:126-138

Novel Approaches Are Needed in Melanoma



Checkpoint inhibition is not sufficient here

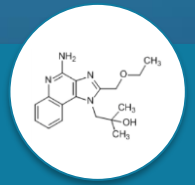
Anti-CTLA4 + anti-PD-1

Anti-PD-1

Anti-CTLA4

Adapted from Ugurel et al. Eur J Cancer 2020; 130:126-138

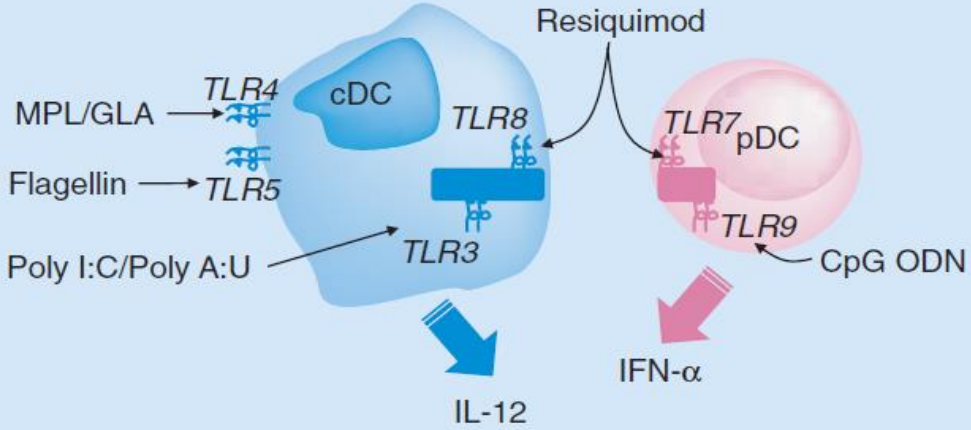
Product Candidates in Oncology



TransCon TLR7/8 Agonist

Resiquimod: TLR7/8 Agonist [1,2]

- Small molecule agonist of both TLR7 and TLR8
  - TLR7: mainly expressed in dendritic cells (DCs), to some extent in B cells, monocytes, macrophages
  - TLR8: primarily expressed in DCs, monocytes, macrophages
- Potent activator of the innate immunity
  - Elevates proinflammatory cytokines
  - Enhances antigen presentation
  - Enhances anti-tumor immunity



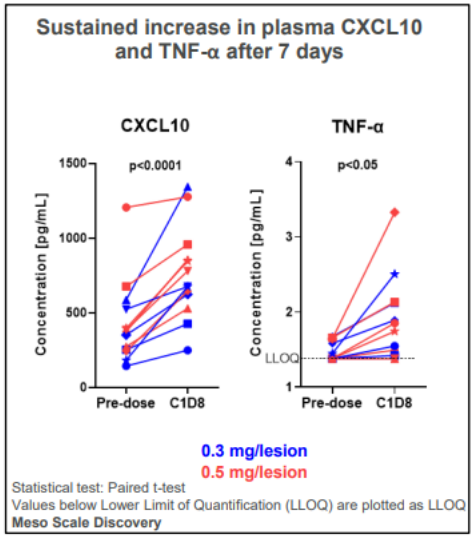
Resiquimod activates dendritic cells, key antigen-presenting cells

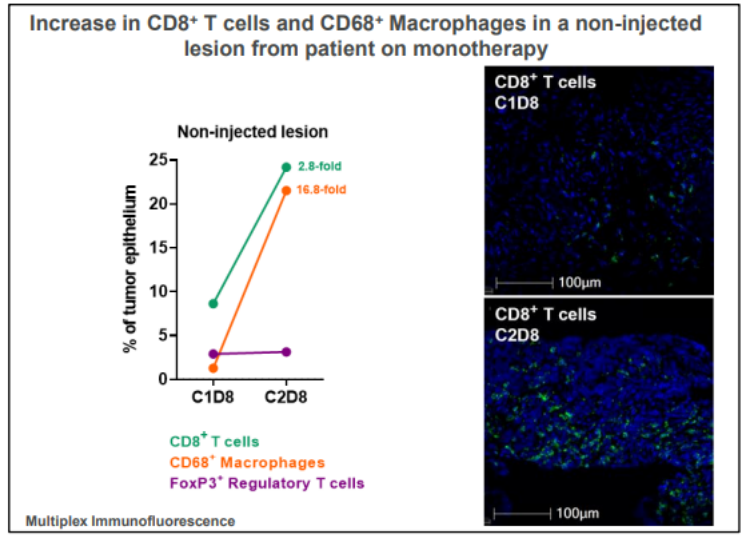
[1] Vasilakos J and Tomai M. *Exp Rev Vaccines*, 2013; 12:809-819. [2] Rook A, et al. *Blood*. 2015;126(25):2765.

transcendIT-101 Oral Presentation at SITC 2022

Intratumoral TransCon TLR7/8 Agonist RP2D declared at 0.5mg/lesion

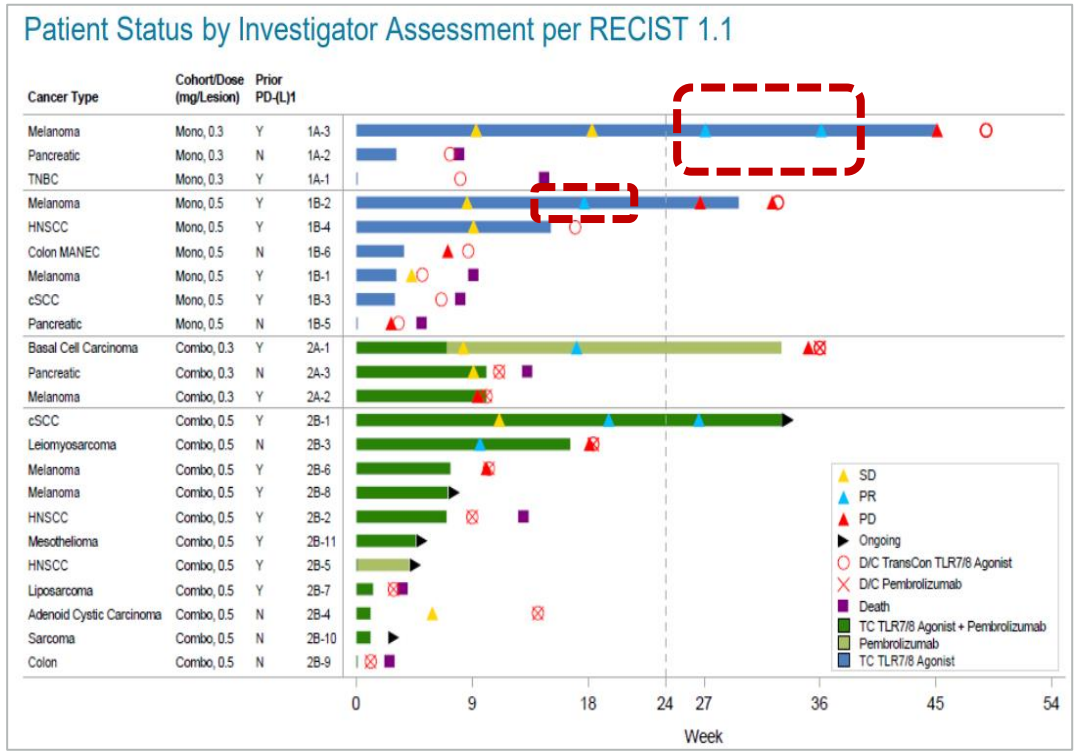
- Generally well-tolerated with 1 DLT (grade 3 injection site reaction) from 23 patients treated in dose escalation cohorts, as monotherapy or in combination with pembrolizumab
- PK data showed low systemic exposure and sustained release of resiquimod over weeks after a single injection
- Biomarker data showed target engagement in injected and non-injected tumors along with sustained systemic immune response
- Clinical activity observed with monotherapy anti-tumor response including abscopal effect

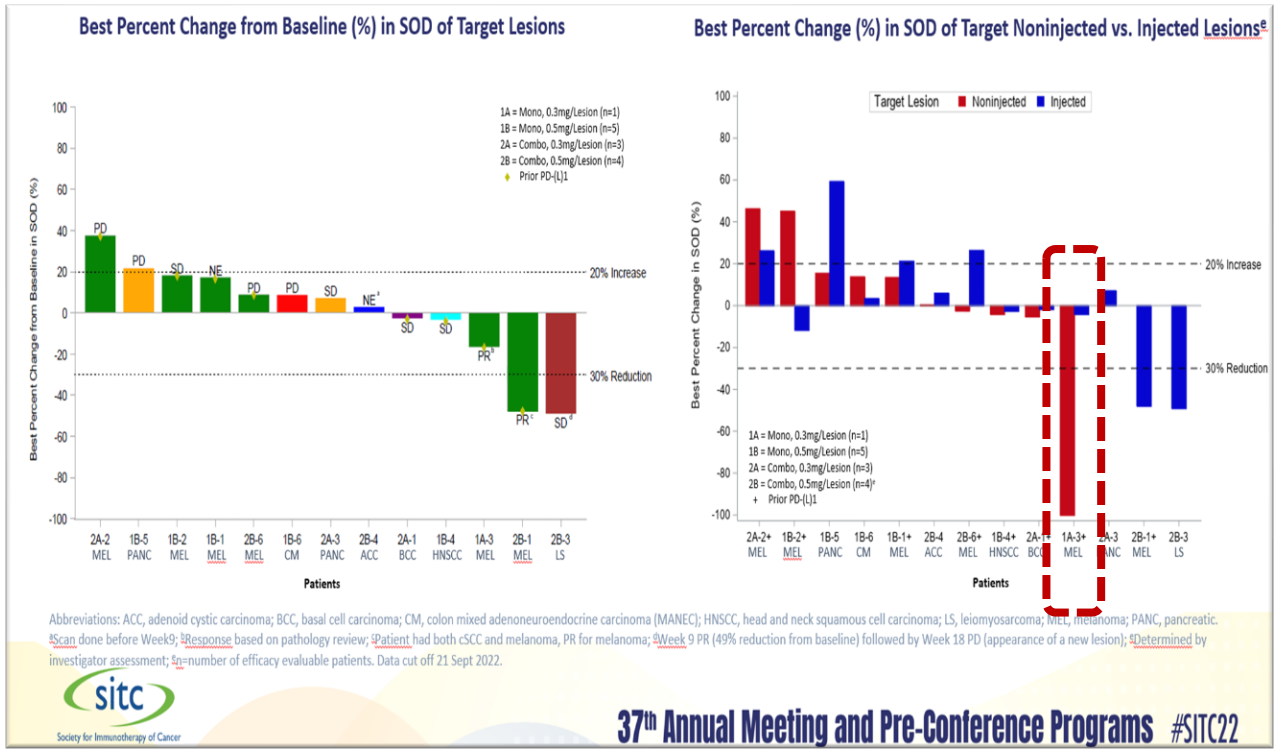




RP2D=recommended phase 2 dose
DLT=dose limiting toxicity

TransCon TLR7/8 Agonist Has Monotherapy Anti-Tumor Activity Locally and Systemically



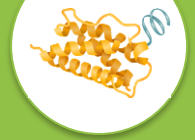


Clinical activity observed with partial response (PR) with monotherapy, including abscopal effect in non-injected lesions, which we continue to see in additional patients

Datacut 21 Sept 2022

Product Candidates in Oncology

IL-2 Selective for the IL-2Rβ/γ



TransCon
IL-2 β/γ

Aldesleukin – Higher Lymphocyte Count Correlated with Better Efficacy

Hospitalization required for administration:

600,000 IU/kg (0.037 mg/kg) IV every 8 hours by for max 14 doses. Following 9 days of rest, the schedule is repeated for another 14 doses, for a max of 28 doses per course, as tolerated. *-Proleukin Product Insert*

Parameters Significantly Associated with Complete Response to Treatment with High-Dose IL-2

Total IL-2 in first course (mean ± SEM, IU/kg):

- Complete responders: 11,171±624
- Noncomplete responders: 9,710 ± 183
- (P_2* = 0.024)

Maximum lymphocytes (mean ± SEM, per mm^3)

- Complete responders: 8,048 ± 900
- Noncomplete responders: 6,514 ± 668
- (P_2* = 0.017)

* Applying the Hochberg correction, these p values are significant at the 0.05 level.

Rosenberg 1998 Ann Surg 228(3):307-19.

Clinical experience with aldesleukin suggests:

Toxicity: vascular leak and severe cytokine release syndrome requiring vasopressors and oxygen support due to IL-2Ra binding to eosinophils, endothelial cells

Normal lymphocyte count range (adult):1000-4800 cells per mm^3

Maximizing IL-2 Therapy Has So Far Been Limited by Toxicity or Insufficient Lymphocyte Expansion and Short Drug Exposure

Copyrighted Image

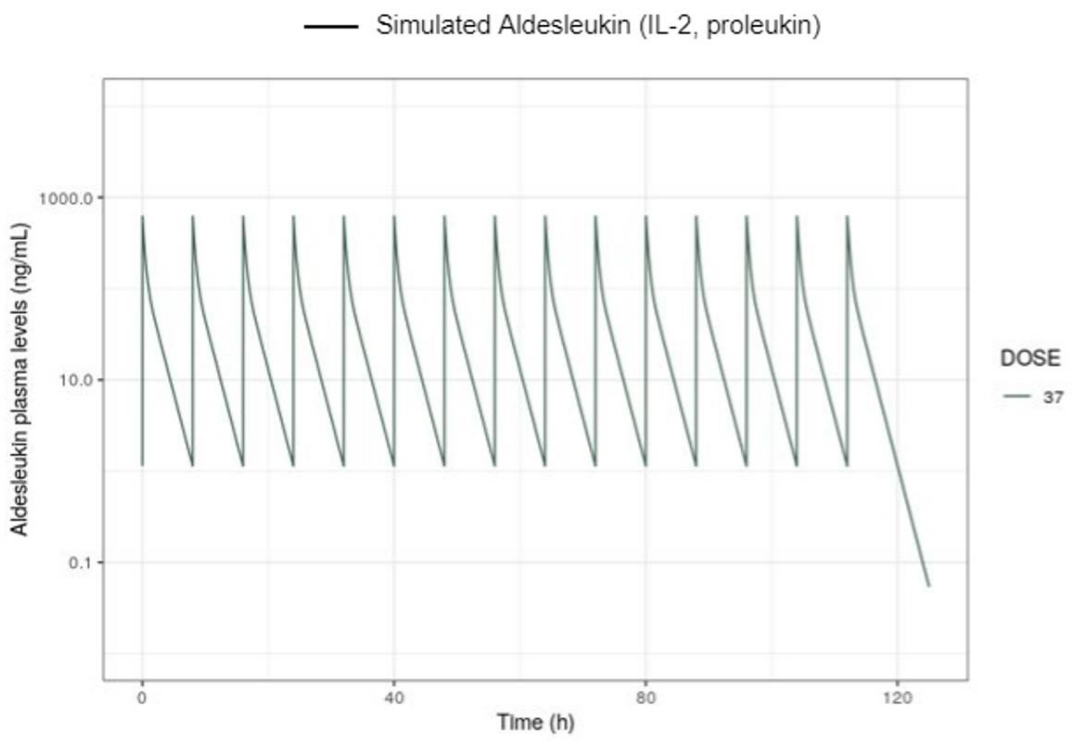
"The goal for IL-2 therapy is typically to administer the maximum number of doses of IL-2 without putting the patient at unacceptable risk for severe, irreversible toxicity."

High dose interleukin-2 (Aldesleukin) – expert consensus on best management practices -2014

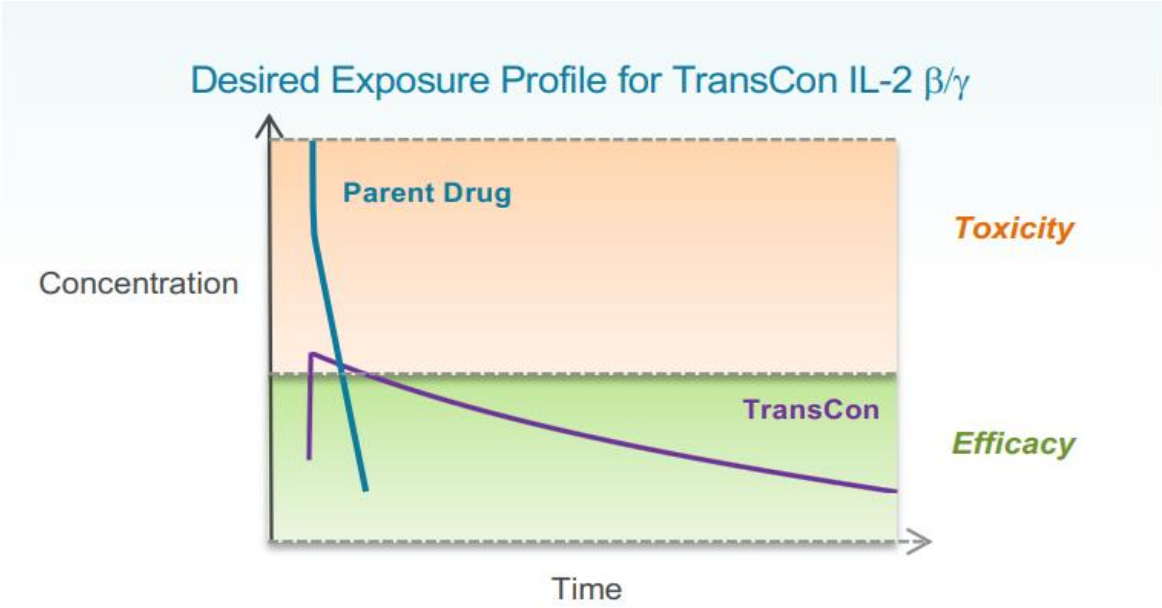
Dutcher et al. Journal for ImmunoTherapy of Cancer 2014, 2:26

Recent clinical programs with IL-2 variants demonstrate improved tolerability and improved PK properties with aim to have better efficacy, but **actual extent (both magnitude and duration) of lymphocyte expansion** has not clearly surpassed that of aldesleukin

Sustained Immunological Activation Potentially Increases Effectiveness While Lowering Toxicity Risk



IV three times a day in ICU for 5 days, rest 9 days, repeat for max 28 doses as tolerated (Proleukin product insert)



IV outpatient once every 3 weeks until progressive disease or unacceptable toxicity

IL-Believe Phase 1/2 Trial Design and Next Steps

Dose Escalation ("3+3" Design)

Monotherapy: *Completed*	Combination with pembrolizumab: *Ongoing*
20 μg/kg	20 μg/kg + pembro
40 μg/kg	40 μg/kg + pembro
80 μg/kg	80 μg/kg + pembro
120 μg/kg	120 μg/kg + pembro
160 μg/kg	

Study status as of 18 May 2023

Ph2 Dose Expansion at RP2D

Combination with pembrolizumab: *Ongoing*

- Cohort 3: TransCon IL-2 β/γ + chemo — **PROC**
- Cohort 4: TransCon IL-2 β/γ + TC TLR 7/8 Agonist — **Post anti-PD-1 Melanoma**
- Cohort 5: TransCon IL-2 β/γ + TC TLR 7/8 Agonist — **2L+ Cervical Cancer**
- Cohort 7: TransCon IL-2 β/γ + chemo + pembro — **Neoadjuvant NSCLC**
- Cohort 6a*: TransCon IL-2 β/γ monotherapy — **Neoadjuvant Melanoma**
- Cohort 6b*: TransCon IL-2 β/γ + pembro — **Neoadjuvant Melanoma**
- Cohort 6c*: TransCon IL-2 β/γ + TC TLR 7/8 Agonist — **Neoadjuvant Melanoma**

***monotherapy arm will only open if either of combination arms passes futility**

PROC = platinum resistant ovarian cancer;
NSCLC = non-small cell lung cancer

Study designed to define maximum tolerated dose and assess preliminary anti-tumor efficacy

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

TransCon IL-2 β/γ Dose Escalation

Monotherapy: *Completed*	Combination with pembrolizumab: *Ongoing*
20 μg/kg n=4; no DLTs	20 μg/kg + pembro n=4; no DLTs
40 μg/kg n=3; no DLTs	40 μg/kg + pembro n=5; no DLTs
80 μg/kg n=5; no DLTs	80 μg/kg + pembro n=5; no DLTs
120 μg/kg n=8, no DLTs	120 μg/kg + pembro enrolling
160 μg/kg n=5, 1 DLT	

Study status as of 18 May 2023

IL Trial Believe

Monotherapy Dose Escalation Demographics	Total N=25
Age (years), median (min, max)	**64 (37, 82)**
Prior Anti-PD(L)1 Therapy (n %)	**9 (36)**
Prior lines of systemic therapies Median (min, max)	**4 (1,15)**
Tumor Types	
HNSCC	**5**
CRC	**3**
Ovarian	**3**
Pancreas	**3**
Triple-negative breast cancer	**2**
Endometrial	**1**
SCLC	**1**
Esophageal	**1**
Cholangiocarcinoma	**1**
Invasive ductal carcinoma (breast)	**1**
Leiomyosarcoma	**1**
Renal	**1**
Uterine leiomyosarcoma	**1**
Rectal	**1**

HNSCC=head and neck squamous cell carcinoma; CRC=colorectal cancer; SCLC=small cell lung cancer

TransCon IL-2 β/γ monotherapy dose escalation portion completed

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TransCon IL-2 β/γ Phase 1 Preliminary Safety Overview

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 (%)
Dose Limiting Toxicity (DLT)	0 (0)	0 (0)	0 (0)	0 (0)	1 (20)
Grade ≥3 TEAEs related to TransCon IL-2 β/γ	1 (25)	0 (0)	0 (0)	0 (0)	4 (80)
TEAEs leading to treatment discontinuation	1 (25)	0 (0)	1 (20)	2 (25)	1 (20)
TEAEs leading to death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

TEAE=treatment-emergent adverse event; G=grade; CRS=cytokine release syndrome

Data cut 28 Apr 2023

**Primary reason for study discontinuation in End of Treatment (EOT) is death due to progressive disease*
***Subject discontinued treatment due to AEs (including CRS, myalgia and worsening cancer pain)*

TransCon IL-2 β/γ monotherapy was generally well-tolerated with effective half-life of at least 35 hours

TransCon IL-2 β/γ Phase 1 Preliminary Safety Overview

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 (%)
Dose Limiting Toxicity (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) Non-serious G4 lymphopenia*	**0 (0)**	**0 (0)**	**0 (0)**	**4 (80)** *(1) G3 Hypoxia* *(2) G3 Worsening CRS* *(3) G3 Anemia, G3 Thrombocytopenia* *(4) G3 Neutropenia*
TEAEs leading to treatment discontinuation	**1 (25)** *(1) G3 Small bowel obstruction not related to study drug*	**0 (0)**	**1 (20)** *(1) G2 CRS* related*	**2 (25)** *(1) G1 CRS** related* *(2) G4 Septic shock not related to study drug*	**1 (20)** *(1) G4 Lung infection not related to study drug*
TEAEs leading to death	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**

TEAE=treatment-emergent adverse event; G=grade; CRS=cytokine release syndrome

Data cut 28 Apr 2023

**Primary reason for study discontinuation in End of Treatment (EOT) is death due to progressive disease*
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TransCon IL-2 β/γ Phase 1 Preliminary Safety Overview

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 (%)
Dose Limiting Toxicity (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) Non-serious G4 lymphopenia*	**0 (0)**	**0 (0)**	**0 (0)**	**4 (80)** *(1) G3 Hypoxia* *(2) G3 Worsening CRS* *(3) G3 Anemia, G3 Thrombocytopenia* *(4) G3 Neutropenia*
TEAEs leading to treatment discontinuation	**1 (25)** *(1) G3 Small bowel obstruction not related to study drug*	**0 (0)**	**1 (20)** *(1) G2 CRS* related*	**2 (25)** *(1) G1 CRS** related* *(2) G4 Septic shock not related to study drug*	**1 (20)** *(1) G4 Lung infection not related to study drug*
TEAEs leading to death	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**

TEAE=treatment-emergent adverse event; G=grade; CRS=cytokine release syndrome

Recommended Phase 2 Dose

Data cut 28 Apr 2023

**Primary reason for study discontinuation in End of Treatment (EOT) is death due to progressive disease*
***Subject discontinued treatment due to AEs (including CRS, myalgia and worsening cancer pain)*

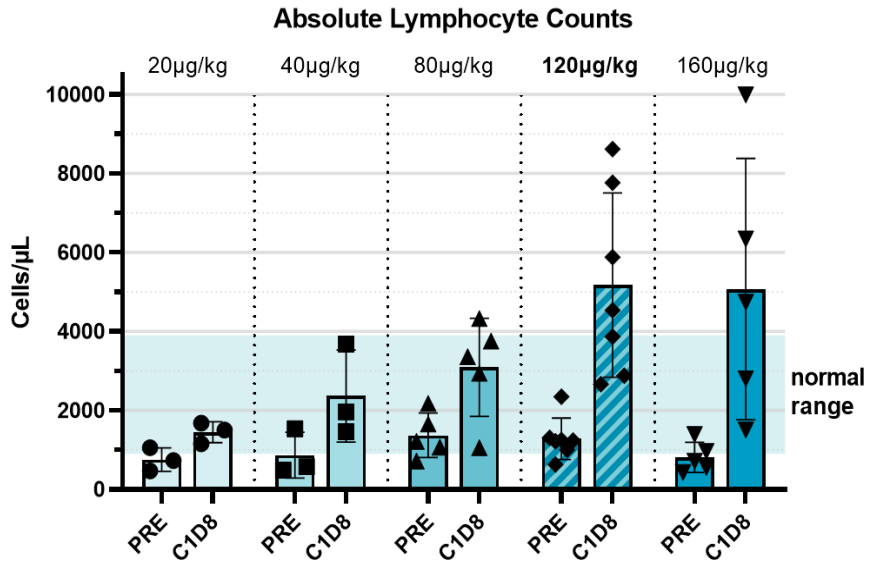
Recommended Phase 2 dose at 120μg/kg IV Q3W showed no G3/4 CRS or vascular leak syndrome

Absolute Lymphocyte Count (ALC) and Eosinophils One Week After First Dosing

Absolute lymphocyte count

ALC on C1D8 (x1000 cells/µL)	20 µg/kg	40 µg/kg	80 µg/kg	120 µg/kg	160 µg/kg
mean	1.4	2.4	3.1	5.2	5.1
median	1.5	2.0	3.4	4.5	4.7

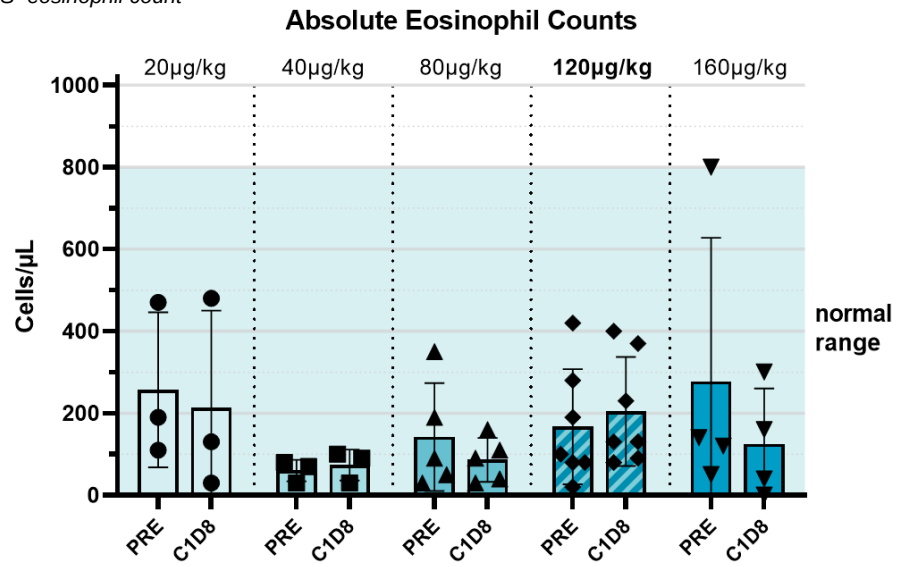
ALC=absolute lymphocyte count



Eosinophils

EOS on C1D8 (x1000 cells/µL)	20 µg/kg	40 µg/kg	80 µg/kg	120 µg/kg	160 µg/kg
mean	0.21	0.07	0.09	0.20	0.13
median	0.13	0.09	0.09	0.13	0.10

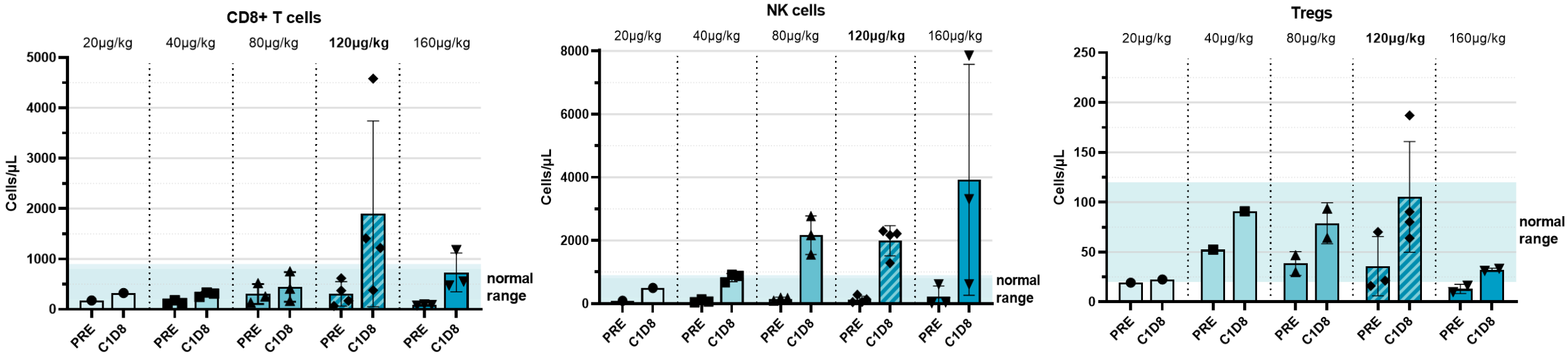
EOS=eosinophil count



Demonstrated clear dose-dependent ALC expansion without effect on eosinophils

Each dot represents a single patient; bar indicates the mean of the values; error bars indicate standard deviation from the mean

Cytotoxic Immune Cells (CD8+ T and NK cells) and Regulatory T (T_{reg}) Cells One Week After First Dosing



Each dot represents a single patient; bar indicates the mean of the values; error bars indicate standard deviation from the mean

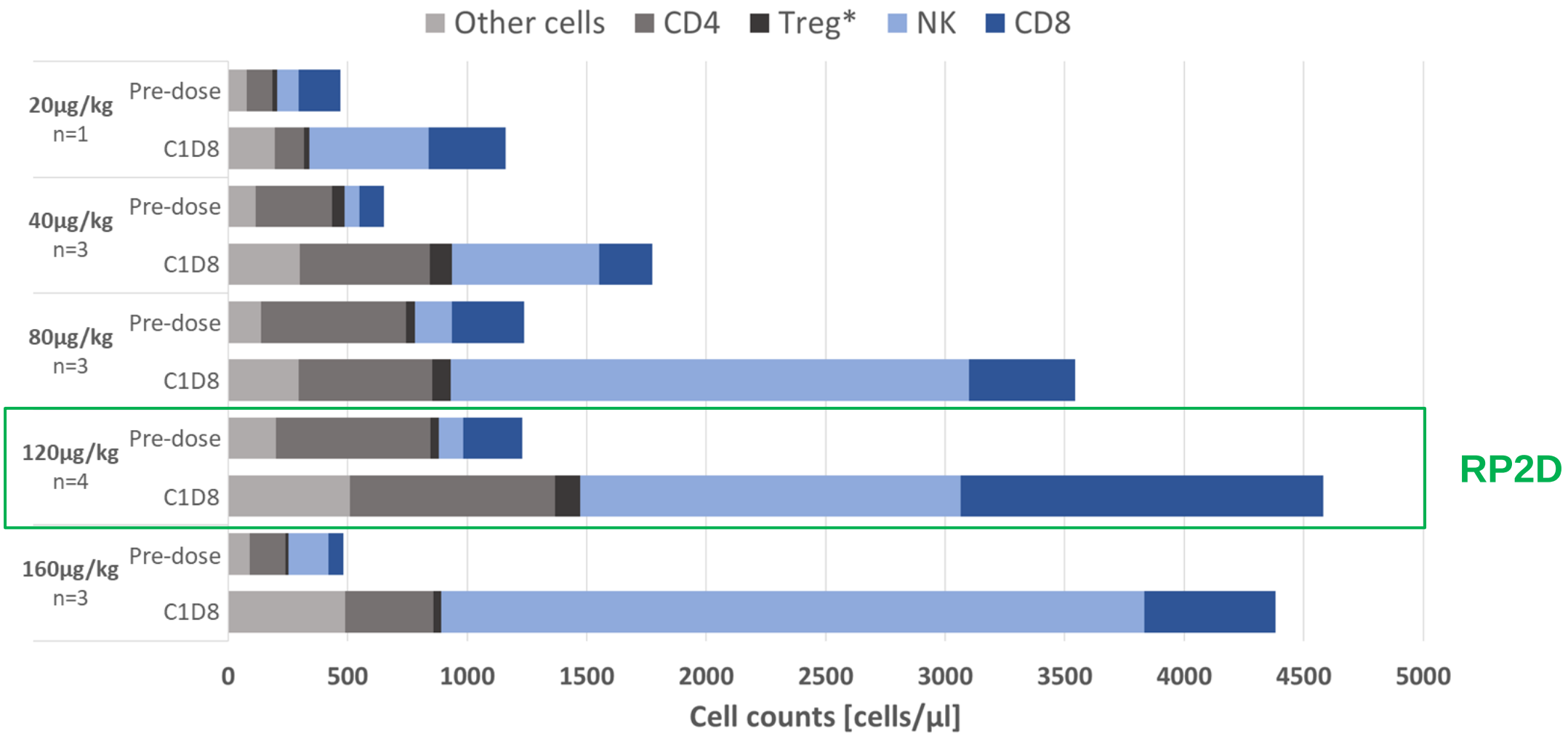
Normal range:
Bofill et al., 1991 - Laboratory control values for CD4 and CD8 T lymphocytes. Implications for HIV-1 diagnosis
Kokuina et al., 2019 - Normal Values of T, B and NK Lymphocyte Subpopulations in Peripheral Blood of Healthy Cuban Adults

Normal range:
Kokuina et al., 2019 - Normal Values of T, B and NK Lymphocyte Subpopulations in Peripheral Blood of Healthy Cuban Adults
Ebbo et al., 2016 - Low Circulating Natural Killer Cell Counts are Associated With Severe Disease in Patients With Common Variable Immunodeficiency

Normal range – calculated from normal range of CD4+ T cells:
Liotta et al., 2010 - Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma
Li et al., 2019 - Increased frequency of regulatory T cells in the peripheral blood of patients with endometrioid adenocarcinoma

Demonstrated clear dose-dependent response on cytotoxic immune cells without significant effect on T_{regs}

TransCon IL-2 β/γ Changes the Lymphocyte Composition Towards a Majority of Cytotoxic Lymphocytes One Week After First Dosing

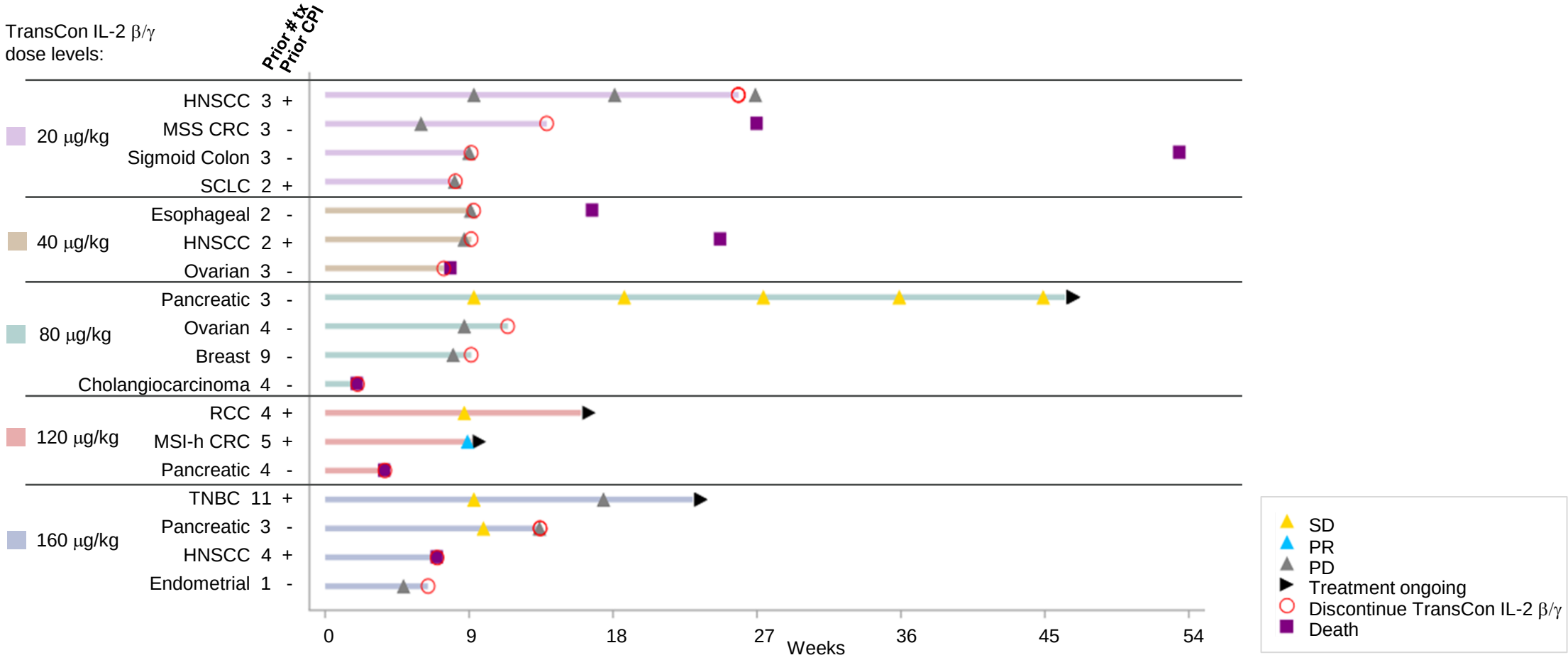


RP2D

Average cell count per dose-level - calculated from ALC and Flow Cytometry results
**Cell count based on all available data*

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

Status of Efficacy-Evaluable Patients Data Cut Apr 28, 2023



Early evidence of clinical benefit in 1 pancreatic cancer with durable stable disease >45 weeks and 1 MSI-h CRC progressed on prior anti-PD1 with PR at first tumor assessment

 # tx= number of lines of systemic treatment; CPI=checkpoint inhibitor; HNSCC=head and neck squamous cell cancer; MSS=microsatellite stable; CRC=colorectal cancer; SCLC=small cell lung cancer; RCC=renal cell carcinoma; MSI-h=microsatellite instability high; TNBC=triple negative breast cancer

Response by Investigator Assessment per RECIST v1.1
Data cut 28 Apr 2023

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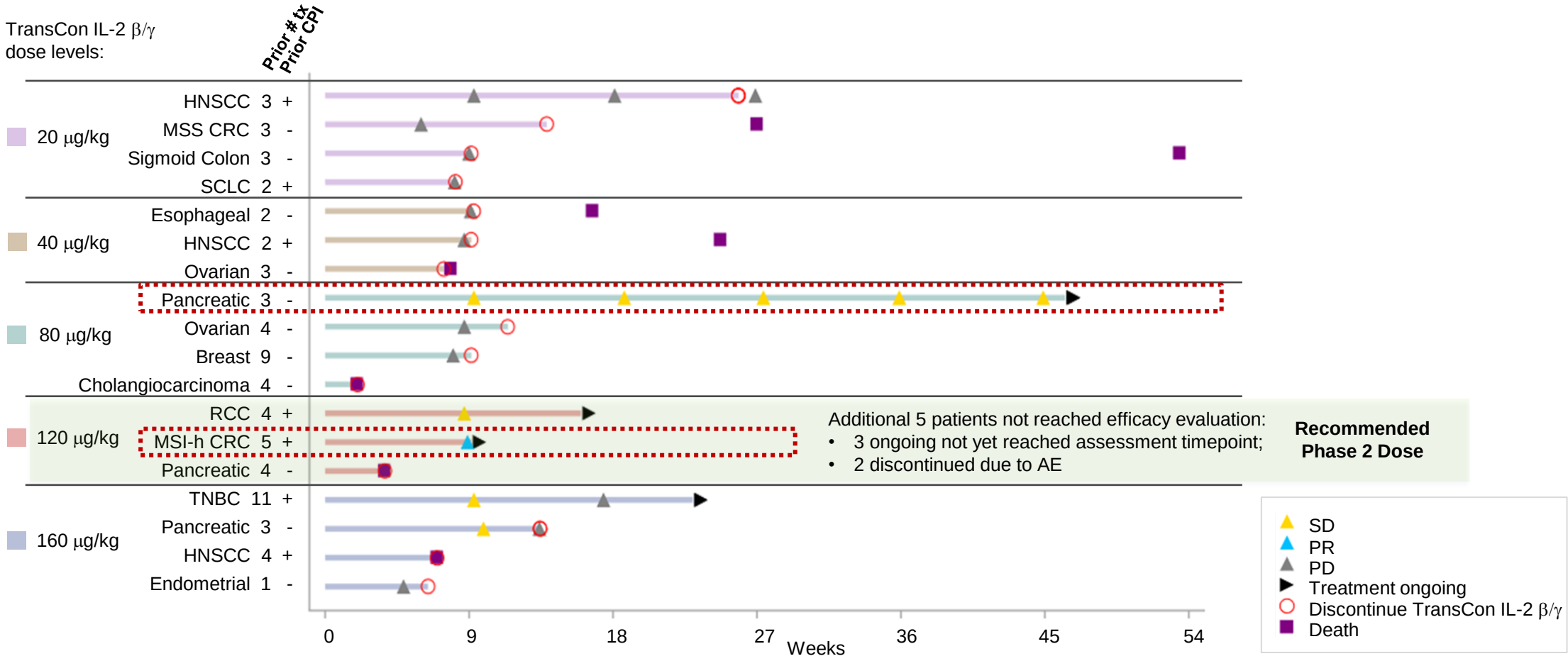
TransCon IL-2 β/γ Phase 1 Monotherapy Dose Escalation

Status of Efficacy-Evaluable Patients Data Cut Apr 28, 2023



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Response by Investigator Assessment per RECIST v1.1
Data cut 28 Apr 2023

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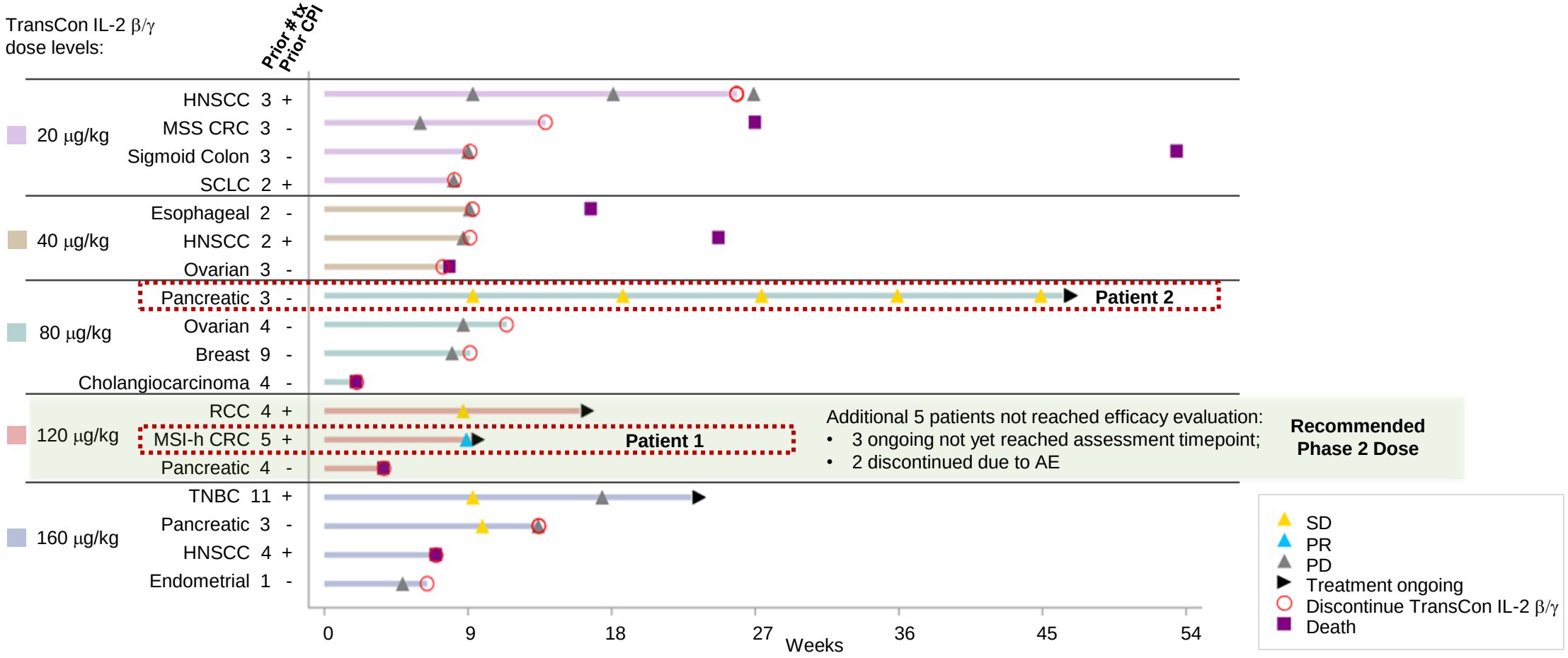
TransCon IL-2 β/γ Phase 1 Monotherapy Dose Escalation

Status of Efficacy-Evaluable Patients Data Cut Apr 28, 2023



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Response by Investigator Assessment per RECIST v1.1
Data cut 28 Apr 2023

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Patient 1: Heavily Pre-treated Metastatic Colorectal Cancer

Patient with metastatic colorectal cancer (CRC):

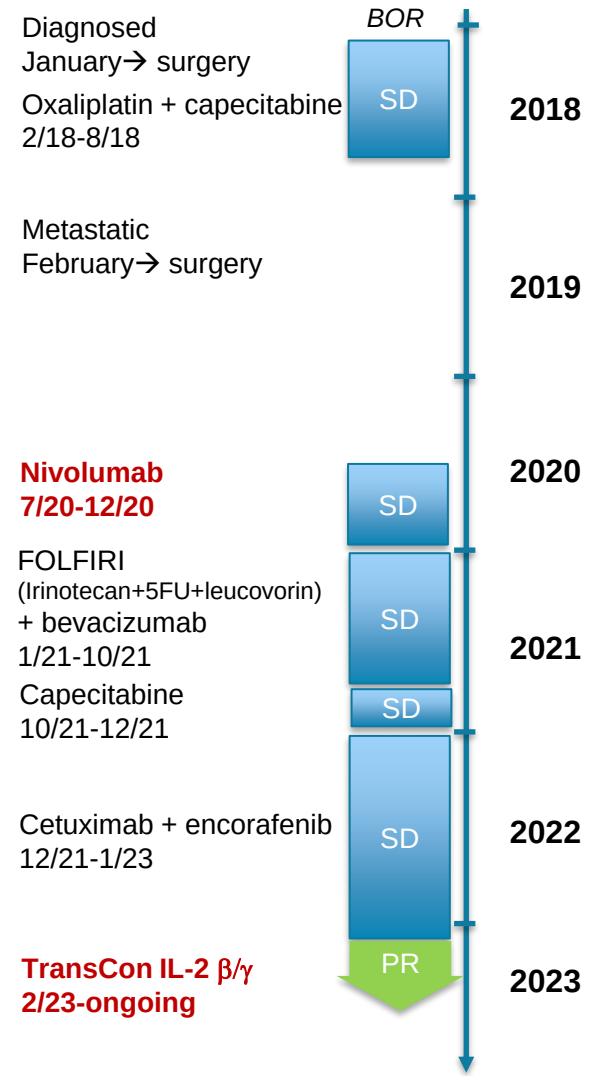
- Tumor genetics: Microsatellite Instability High (MSIh); BRAF V600E
- Prior 5 lines of systemic treatments, including nivolumab, all with Best Overall Response of Stable Disease (SD)
- Started on TransCon IL-2 β/γ monotherapy 120μg/kg every 3 weeks since February 2023, now ongoing after 4 cycles
- Treatment related adverse events: Grade 2 fever, Grade 2 myalgia, Grade 1 rash, Grade 1 pruritis

Tumor assessment at Week 9: 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	uPR

Partial Response on monotherapy TransCon IL-2 β/γ



Datacut 28 April 2023

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

Patient 2: Heavily Pre-treated Metastatic Pancreatic Cancer

- Patient who progressed after 3 prior lines of systemic treatment
  - Widely metastatic pancreatic cancer including liver and lung involvement
- TransCon IL-2 β/γ monotherapy treated since June 2022
  - Long stable disease ongoing ~1 year on treatment after 13 cycles

Datacut 17 May 2023

Recommended Phase 2 Dose (RP2D) for TransCon IL-2 β/γ Determined from Multiple Observations

TransCon IL-2 β/γ monotherapy at 120 μg/kg IV Q3W, outpatient

- Safety Profile: generally well-tolerated with no DLT out of 8 patients dosed; no vascular leak syndrome; no grade 3 or 4 cytokine release syndrome
- Long effective half life with low C_{max}
- Expands local and systemic cytotoxic immune effector cells (CD8+ T and NK cells) without clear effect on T_{regs} and eosinophils
- Clinical benefit observed with monotherapy in heavily pre-treated patients

Aiming to cure more cancer patients safely with amplified and durable immune activation

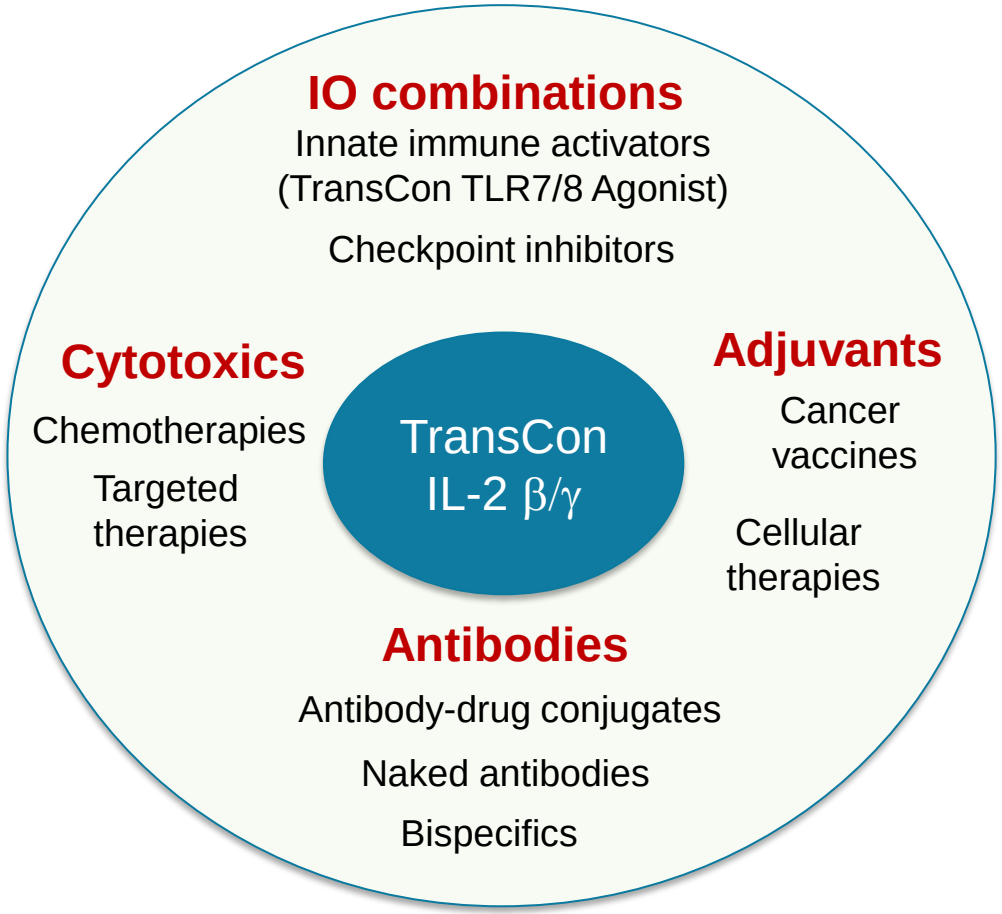
Next Steps: Phase 2 Indication-Specific Cohorts

- First indications selected for speed to meaningful endpoint readout and current treatment landscape
- Phase 2 dose expansion cohorts currently enrolling in 7 different tumor types; ~40 patients per cohort
  - Melanoma (neoadjuvant and post anti-PD1)
  - cSCC (neoadjuvant)
  - HNSCC (1/2L metastatic)
  - Cervical (2/3L metastatic)
  - Other HPV-associated (1/2L metastatic)
  - NSCLC (neoadjuvant)
  - PROC (metastatic)
- Randomized Phase 2 trial in neoadjuvant HNSCC to start this year
- Topline/interim analysis from Phase 2 dose expansion cohorts expected in 2024

Broad clinical development plan aiming to show meaningful clinical activity across various indications

1/2L=1st or 2nd line; 2/3L=2nd or 3rd line; HNSCC=head and neck squamous cell cancer; cSCC=cutaneous squamous cell cancer; HPV=human papilloma virus; NSCLC=non-small cell lung cancer; PROC=platinum resistant ovarian cancer

Multiple Combination Opportunities to Optimize Treatment



TransCon IL-2 β/γ has potential to become a backbone agent in oncology

Oncology Program Summary and Future Directions

- **TransCon IL-2 β/γ**
  - Phase 1 monotherapy dose escalation complete with RP2D determined at 120μg/kg IV every three weeks in May 2023
  - Clinical activity observed with monotherapy anti-tumor response in CRC and long stable disease in pancreatic cancer
  - TransCon IL-2 β/γ has the potential to become a backbone agent in oncology with current developments including subcutaneous formulation with goal for adjuvant treatment setting
- **TransCon TLR7/8 Agonist**
  - RP2D for monotherapy and combination with anti-PD1 determined at 0.5mg/lesion last fall
  - Clinical activity observed with monotherapy anti-tumor response including abscopal effect
- **TransCon IL-2 β/γ and TransCon TLR7/8 Agonist** both demonstrated safety and single-agent clinical activity as key attributes for combinability with various other agents and treatment modalities
  - Enrollment in the transcendIT-101 and IL-Believe trials continuing in Phase 2 Dose Expansion at RP2D in indication-specific cohorts
- Continue to create **potential best-in-class** differentiated product candidates using TransCon Technologies

Aiming to cure more cancer patients with amplified and durable immune activation

Investigator Perspectives

Diwakar Davar, M.D., Associate Professor
Clinical Director of Melanoma and Skin Cancer Program, University of Pittsburgh Medical Center (UPMC), Hillman Cancer Center

Disclosures and Funding – Dr. Davar

- **Grants/Research Support (institutional):** Arcus, CellSight Technologies, Immunocore, Merck, Regeneron Pharmaceuticals Inc., Tesaro/GSK.

- **Consultant:** ACM Bio, Ascendis Pharma, Clinical Care Options (CCO), Gerson Lehrman Group (GLG), Merck, Medical Learning Group (MLG), Xilio Therapeutics

- **CE Speakers' Bureau:** Castle Biosciences.

- **Intellectual Property:**

US Patent 63/124,231, "Compositions and Methods for Treating Cancer", Dec 11, 2020

US Patent 63/208,719, "Compositions and Methods For Determining Responsiveness to Immune Checkpoint Inhibitors (ICI), Increasing Effectiveness of ICI and Treating Cancer", June 9, 2021

Metastatic Pancreatic Cancer on TransCon IL-2 β/γ Monotherapy

Case study: 67-year-old male with metastatic pancreatic cancer.

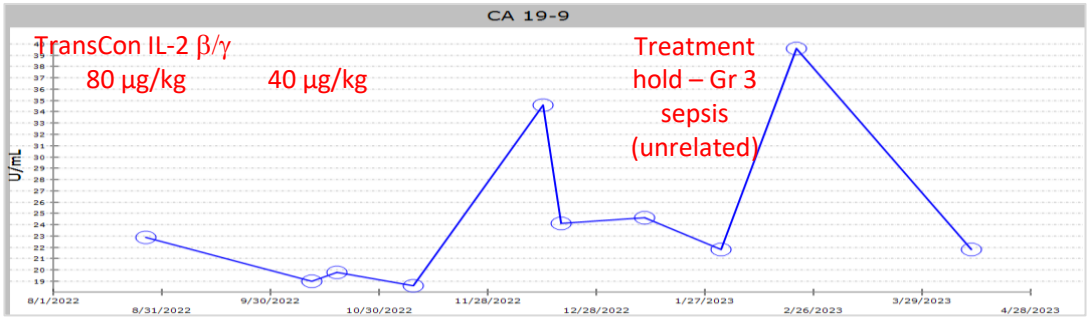
Tumor genetics: Microsatellite Stable (MSS); KRAS G12V

Prior 3 lines of systemic treatments with Progressive Disease (PD) as Best Overall Response

Started on TransCon IL-2 β/γ monotherapy 80μg/kg every 3 weeks since June 2022, now ongoing after 13 cycles

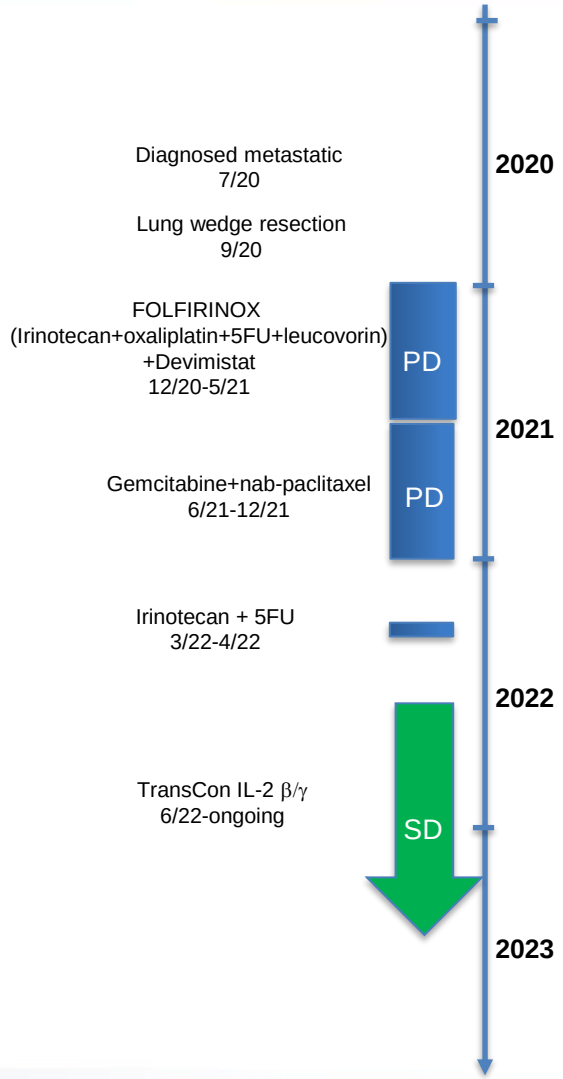
- Dose reduced to 40μg/kg since cycle 5 in September 2022
- Tocilizumab added with cycle 8

Encouraging CA19-9 trend shown in blue (tumor marker for pancreatic cancer)



Treatment related adverse events:

- No grade 3 or above
- Grade 2: cytokine release syndrome, Infusion related reaction, white blood cell count decreased, neutrophil count decreased, lymphocyte count decreased`



mm=millimeter; RECIST v1.1=Response Evaluation Criteria for Solid Tumors version 1.1; PR=partial response; CR=complete response; PD=progressive disease; SD=stable disease

Metastatic Pancreatic Cancer with Long Stable Disease on TransCon IL-2 β/γ Monotherapy

Visit	Sum of Diameters in mm (% change from baseline)	Target Lesion Response	Non-target Response	New Lesion	RECIST v1.1 Overall Response
Baseline	64.6				
Week 9	63.5 (-2%)	SD	Non-CR/Non-PD	No	SD
Week 18	70.4 (+9%)	SD	Non-CR/Non-PD	No	SD
Week 27	70.1 (+9%)	SD	Non-CR/Non-PD	No	SD
Week 36	71.2 (+10%)	SD	Non-CR/Non-PD	No	SD
Week 45	66.9 (+4%)	SD	Non-CR/Non-PD	No	SD

Tumor assessments every 9 weeks since first dosing in June 2022 showing Stable Disease (SD), ongoing past Week 45

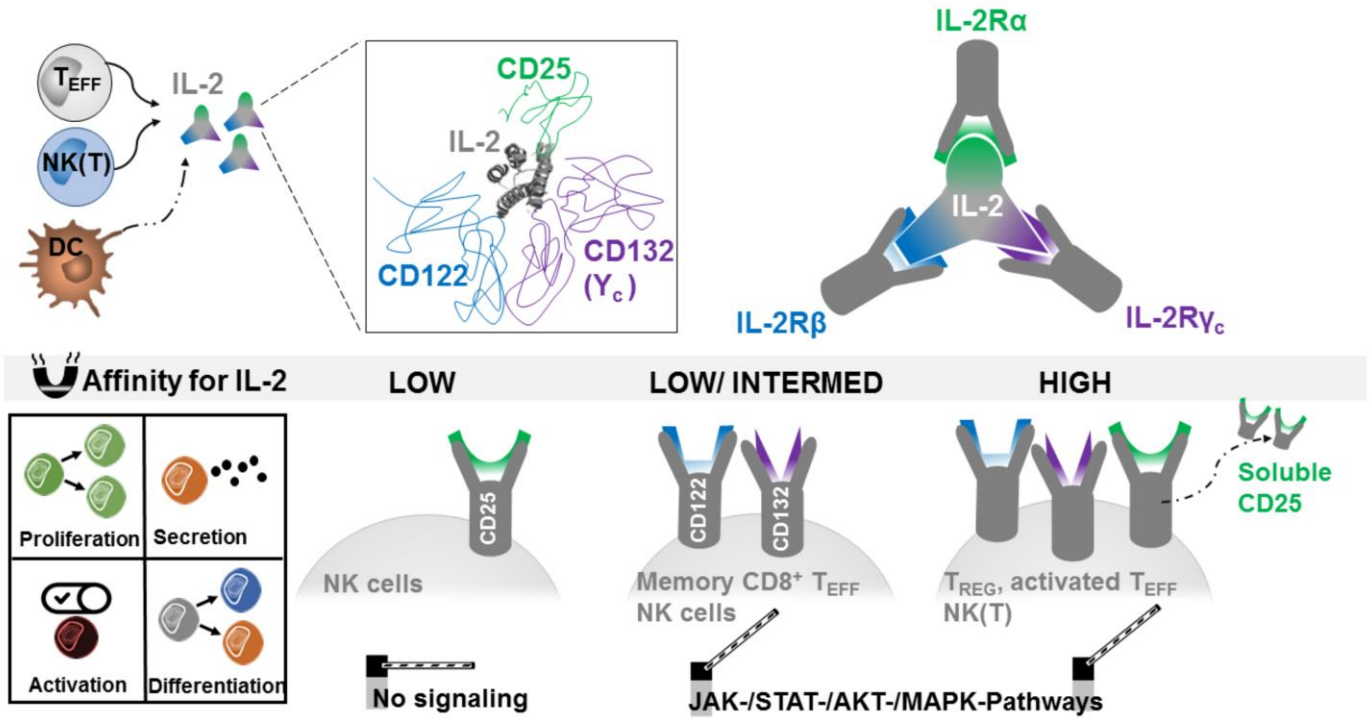
- Target lesions: pancreatic mass, 2 lung lesions
- Non-target lesions: liver, pancreas, lung, spleen, multiple lymph nodes

Heavily pre-treated, widely metastatic pancreatic cancer including liver and lung involvement on TransCon IL-2 β/γ monotherapy experiencing long stable disease ongoing ~1 year on treatment

Datacut 29 April 2023

mm=millimeter; RECIST v1.1=Response Evaluation Criteria for Solid Tumors version 1.1; PR=partial response; CR=complete response; PD=progressive disease; SD=stable disease

2nd Generation IL-2 Agonists Aim to Harness T cells and NK cells



Augmenting PD-1 Efficacy without Additional Costim (CD28) or Coinhibition (CTLA-4, TIM-3, LAG-3)

- Interleukin-2 (IL-2) is a T cell growth factor that signals through a complex network of receptors of varying affinity with effects upon Tregs, T effector cells and memory T cells.
- PD-1+TCF-1+ stem-like CD8+ T cells are ***not fate-locked***.
- Antigen-specific CD8+ T cells express increased levels of the high affinity IL-2 trimeric receptor; and combination therapy demonstrates synergy in LCMV and cancer models preclinically.[2-3]
- Synergy is dependent upon CD25 engagement,[2] but can be overcome by binding of IL-2 to PD-1 and IL-2Rβγ on the same cell in *cis.*[3]

REF: [1]Raker VR, Cells 2020; [2]Hashimoto M, Nature 2022; [3]Deak LC, Nature 2022

2nd Generation IL-2 Agonists Aim to Harness T cells and NK cells

Drug (Company)	Description	Phase	Indications
Nemvaleukin alfa (Alkermes)	IL-2-CD25 fusion	3	• Ovarian cancer (ARTISTRY-7)
		2	• Cutaneous and mucosal melanoma (ARTISTRY-6)
		1	• Single agent dose-escalation and combination with pembro (ARTISTRY-1)[1]
TransCon IL-2 (Ascendis)	PEGylated IL-2 muteins	1/2	Pending
AU-007 (Aulos)	Anti-IL-2 mAb	1/2	Pending
ANV419 (Anaveon)	IL-2-anti-IL-2 fusion	1/2	Pending
BNT151 (BioNTech)	mRNA-encoded IL-2 mutein	1/2	Pending
MDNA11 (Medicenna)	Albuminated IL-2 mutein	1/2	Pending
XTX-202 (Xilio)	Masked IL-2 mutein	1/2	Pending
CUE-101 (Cue Biopharma)	E7-pHLA-IL-2-Fc fusion protein	1	HPV+ tumors[2]
NL-201 (Neoleukin)	IL-2 and IL-15 mimic without CD25-binding interface	1	Pending
MK-1484 (Merck)	β/γ-selective IL-2 mutein	1	Pending
RG6279 (Roche)	IL-2–anti-PD-1 fusion protein	1	Pending
SHR-1916 (Jiangsu Hengrui)	PEGylated IL-2 muteins	1	Pending
STK-012 (Synthekine)	α/β-selective IL-2 mutein	1	Pending

Not included:

- Bempegaldesleukin (pegylated IL-2 mutein). Negative phase 3 (PIVOT IO-001) in 1L metastatic melanoma (ORR 28% bempeg/nivo vs. 36% nivo).[3]
- SAR444245/THOR-707 (pegylated IL-2 mutein). Phase II (Q3W dosing) combination data reported.[4] Program deprioritized and dose-intensification trial announced.

Trends:

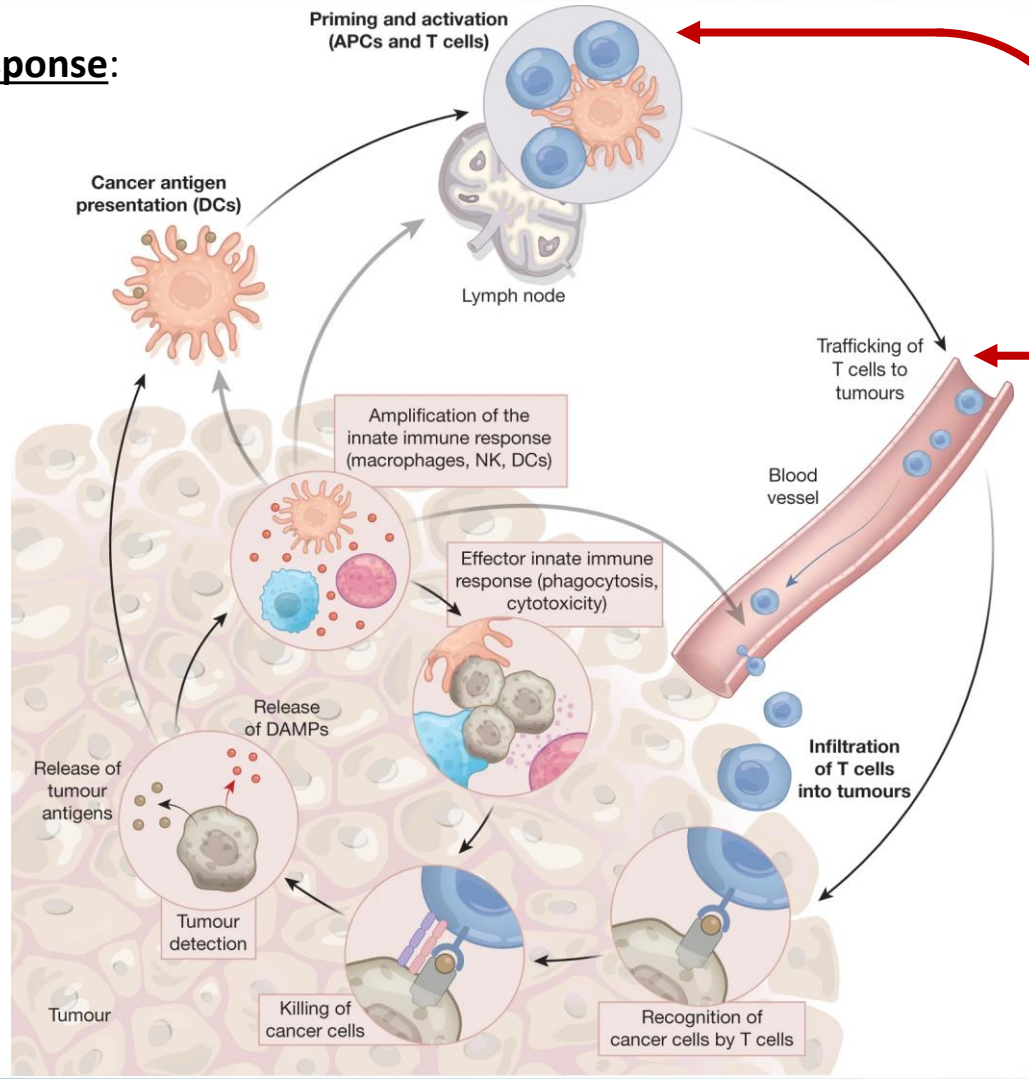
- POC generation in melanoma and RCC given original indications for aldesleukin.[5,6]
- Expansions in tumor types such as PROC and mucosal melanoma wherein single-agent PD-1 activity is low.
- Unexplored indications: neoadjuvant settings (melanoma, NSCLC) and other cutaneous tumors where CTLA-4 has not added to PD-1 (cSCC, MCC).

REF: [1]Vaishampayan UN, ASCO 2022; [2]Chung CH, ASCO 2022; [3]Diab A, ESMO 2022; [4]Falchook G, SITC 2021; [5]Atkins MB, J Clin Oncol 1999; [6]Klapper JA, Cancer 2012

Overcoming Immune Checkpoint Inhibitor Resistance in Cancer with Innate Agonists[1]

Key cells involved in innate response:

- NK cells
- DC
- Macrophages



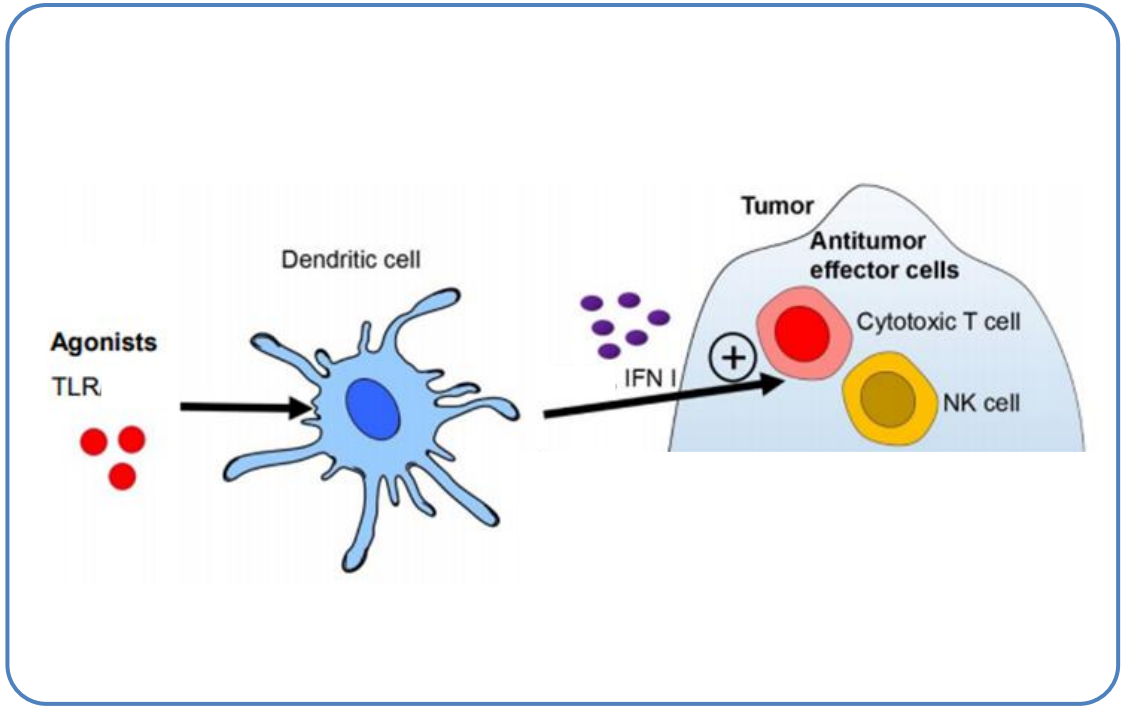
Harnessing innate immunity in cancer therapy

- Targeting anti-microbial immunity for anti-tumor effects (**TLR7/8/9**, ~~RIG-I, STING, NLRP3~~)
- Amplification of immune response (APC activation; co-stimulatory signals; **cytokines such as IL-2, IL-12, IL15**)
- Targeting immune suppression within tumor by targeting immune suppressive factors (A_2AR, CD39/CD73, IDO, TGFβ, EP4, arginase) or targeting suppressive cells (C5aR1, IL-1β, IL-1α, CXCR2, CCR2, CCR5, ApoE, STAT3, PI3Kγ, CSF-1R)

[1]Demaria, Nature 2019

Toll-Like Receptors (TLRs): Well-Validated Targets for Activation of Innate and Adaptive Immunity[1]

- Activate innate immunity in particular antigen presenting cells (APCs)
- Prime and expand cytolytic and helper T cells
- Activate and expand cytotoxic lymphocytes
- Resiquimod has been clinically evaluated as a potent TLR7/8 Agonist[2,3]



1. Bourquin C, et al. *Pharmacol Res*, 2020; 154:104192
2. Vasilakos J and Tomai M. Exp Rev Vaccines, 2013; 12:809-819.
3. Rook A, et al. Blood. 2015;126(25):2765.

TLRs activate several key pathways critical in host defense against tumors

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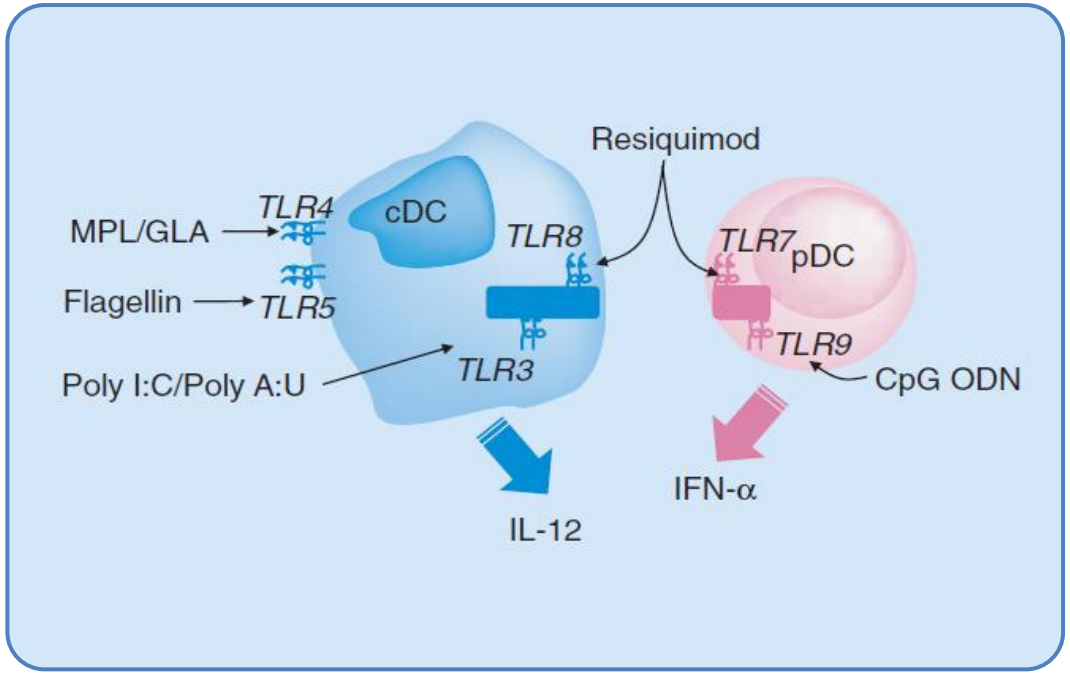
Resiquimod: TLR7/8 Agonist[1,2]

- Small molecule agonist of both TLR7 and TLR8
  - TLR7: mainly expressed in plasmacytoid dendritic cells (pDCs), to some extent in B cells, monocytes, macrophages and conventional dendritic cells (DCs)
  - TLR8: primarily expressed in conventional DCs, monocytes, macrophages and myeloid DCs
- Potent activator of the innate immunity
  - Elevates proinflammatory cytokines: e.g. Type I IFNs, IL-12, TNF-α and chemokines (e.g.CXCL10, CCL2)
  - Enhances antigen presentation: upregulated MHC, costimulatory molecules (e.g. CD80/86)
  - Enhances anti-tumor immunity



[1] Vasilakos J and Tomai M. *Exp Rev Vaccines*, 2013; 12:809-819.
[2] Rook A, et al. *Blood*. 2015;126(25):2765.

Resiquimod activates both conventional DCs and pDCs

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transcendIT-101 Trial Open Cohorts

Phase 1/2, Open-label, Dose Escalation and Dose Expansion Study of TransCon TLR7/8 Agonist Alone or in Combination with Pembrolizumab in Participants with Locally Advanced or Metastatic Solid Tumor Malignancies (ClinicalTrials.gov: NCT04799054)

Dose Optimization (n~6 per cohort)

Part 1: Monotherapy
Any solid tumor, any line

- RP2D Q6W
- RP2D Q3W X 4

→ Schedule based on response

Part 2: Combination Therapy
Indications with known CPI activity

- RP2D Q6W
- RP2D Q3W X 4

→ Schedule based on response

Dose Expansion

Part 3: Combination with Pembrolizumab[a], Dose-Expansion
Indication-specific cohorts

Cohorts 3a and 3b: ≤ 1 line of prior treatment for recurrent metastatic disease

- Cohort 3a: HNSCC (n~23+25[b])
- Cohort 3b: Other HPV-associated tumor types (n~23+25[b])

Cohorts 3c and 3d: no prior treatment for newly diagnosed, resectable disease

- Cohort 3c: Neoadjuvant melanoma (n~17+19[b])
- Cohort 3d: Neoadjuvant cSCC (n~23+14[b])

RP2D = Intratumoral 0.5 mg/lesion every 3 weeks

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transcendIT-101 Safety and Pharmacokinetics Overview

Safety:

- TransCon TLR7/8 Agonist was generally well-tolerated with a low incidence of DLTs (1 grade 3 injection site reaction) from 23 patients treated in dose escalation cohorts, as monotherapy or in combination with pembrolizumab
- All TEAEs related to TransCon TLR7/8 Agonist were grades 1 and 2, except 1 grade 3 injection site reaction
- No TEAEs leading to study drug withdrawal or death

Data cut 27Jan23

Pharmacokinetics (PK):

- Resiquimod plasma concentrations: very low resiquimod C^{max} (relative to levels associated with cytokine release syndrome) and no interaction with pembrolizumab
- Mean systemic half-life ~ 9 days
- No accumulation of resiquimod on dosing every 3rd week

Data cut 21Sep22

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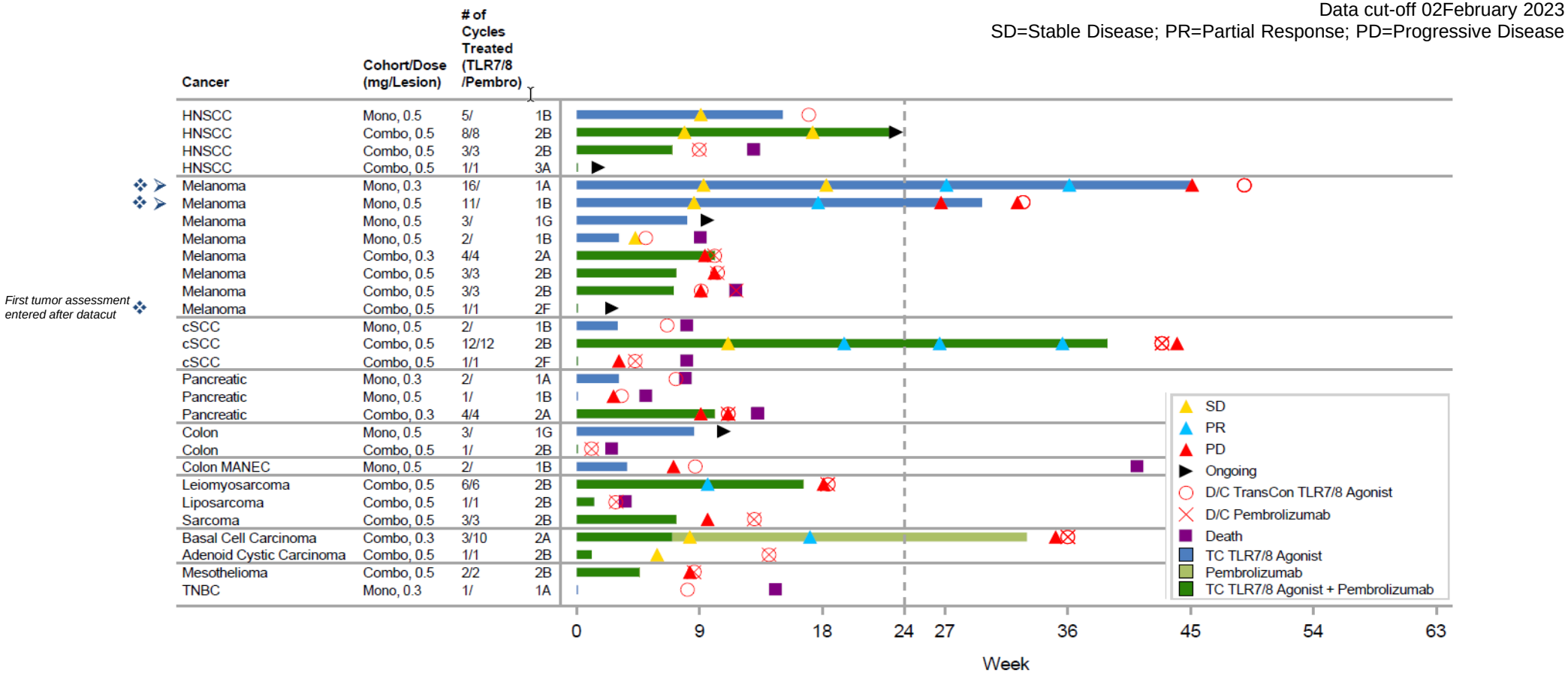
Patient Status by Investigator Assessment per RECIST v1.1 (by indication)

Data cut-off 02February 2023
SD=Stable Disease; PR=Partial Response; PD=Progressive Disease



First tumor assessment entered after datacut

In TransCon TLR7/8 Agonist monotherapy cohorts:

- **2 of 11 (18%) participants had a partial response (1 confirmed and 1 unconfirmed) and**
- **3 of 11 (27%) participants had complete response (CR) in non-injected lesion(s) (i.e. abscopal responses)**

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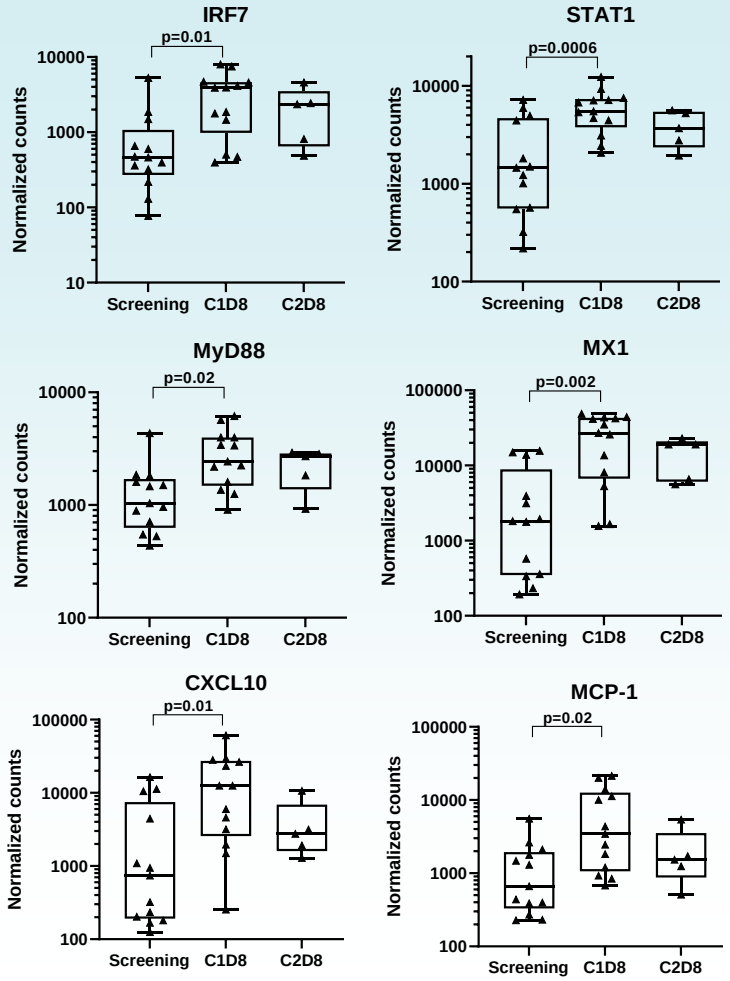
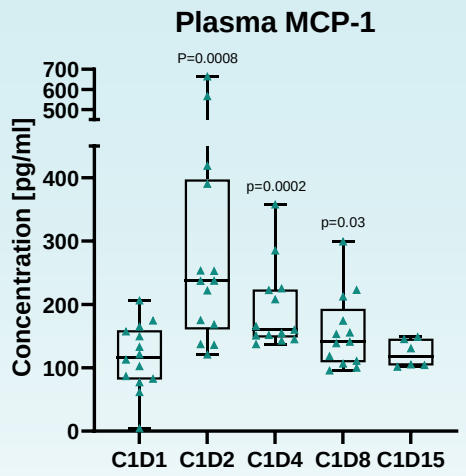
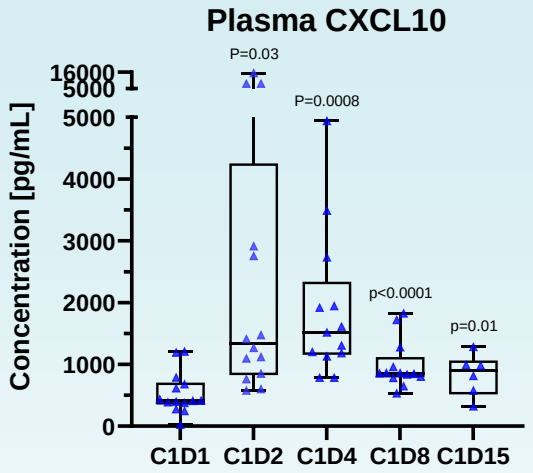
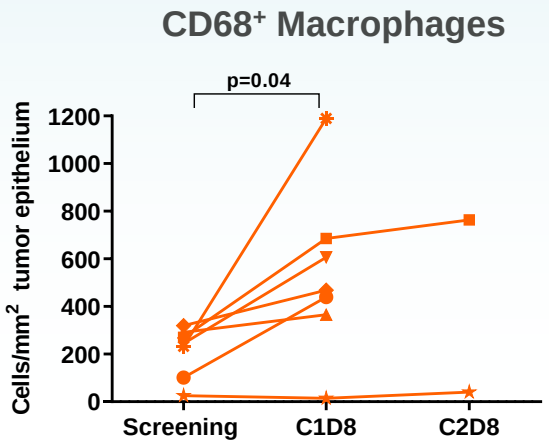
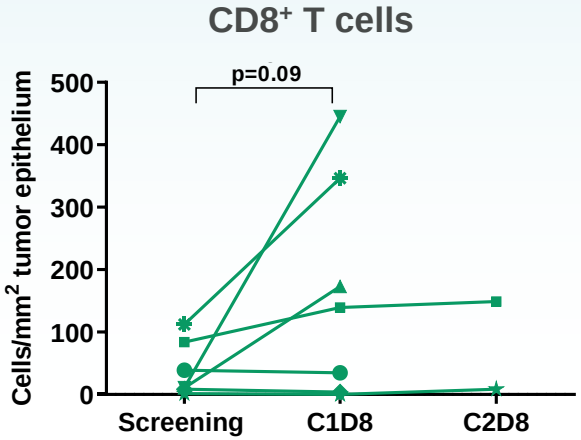
Pharmacodynamic Markers Confirm TransCon TLR7/8 Agonist Target Engagement and Mechanism of Action











Induction and sustained elevation of intratumoral TLR7/8 and Type I IFN pathway gene expression

Intratumoral recruitment of Macrophages and CD8+ T cells

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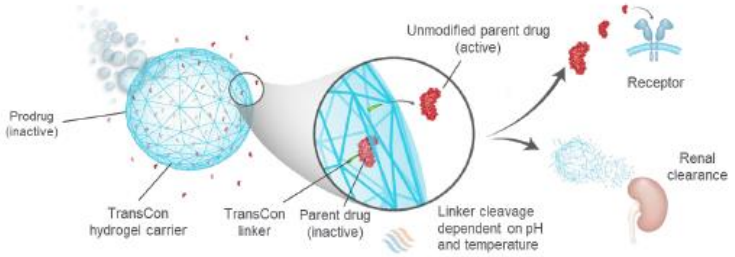
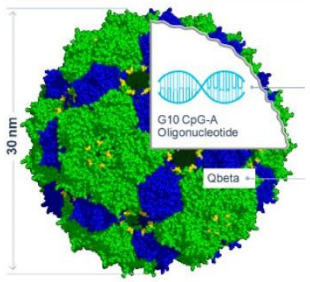
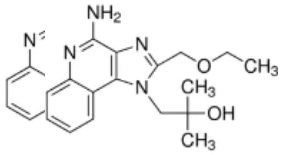
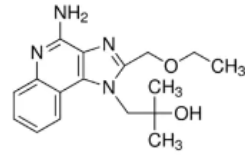
Main Classes of TLR Agonists in Clinical Development

Intratumoral TLR7/8 agonist Sustained Release	Systemic TLR7/8 agonist	Intratumoral TLR9 agonist VLP	Systemic TLR9 agonist mAb conjugate	Intratumoral TLR7/8 agonist
TransCon TLR7/8 agonist	**BDB001**	**Vidutolimod**	**TAC-001**	**NKTR-262**
ascendis pharma	Seven&Eight Biopharma	REGENERON CHECKMATE PHARMACEUTICALS	TALLAC THERAPEUTICS	NEKTAR
	**Salt form Resiquimod**			Discontinued
				

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Main Classes of TLR Agonists in Clinical Development

TLR agonist and molecule engineering	Sustained exposure	Schedule	Route of administration	Limited systemic exposure	Early and sustained CXCL10 levels	Indications under clinical evaluation and combination treatment	Development status
TransCon TLR7/8 Agonist	✓	Q3W or Q6W	Intratumoral	✓	✓	transcendIT-101 - HNSCC and other HPV-associated cancers with pembrolizumab - Neoadjuvant melanoma and neoadjuvant cSCC with pembrolizumab IL-Believe - Post anti PD-1 melanoma & 2L cervical cancer with TransCon IL-2β/γ - Neoadjuvant melanoma with TransCon IL-2β/γ BelievelT-201 - Neoadjuvant HNSCC with pembrolizumab or TransCon IL-2β/γ	Phase 1/2
BDB001 (Modified Resiquimod)	✗	Q1W	Intravenous	✗	✗	Advanced solid tumors with atezolizumab and radiation PD-(L)1 refractory tumors	Phase 2
Vidutolimod (VLP, TLR9 agonist, CpG oligonucleotide)	✗	Q1W induction (7 weeks) Q3W following cycles	Intratumoral	✓	✗	Advanced melanoma with nivolumab cSCC, BCC, Merkel, NSCLC with cemiplimab Metastatic castration resistant prostate cancer with nivolumab	Phase 2
TAC-001 (TLR9 agonist T-CpG, conjugated with CD22 targeting mAb)	✗	Q2W	Intravenous	✗	✗	Advanced or metastatic solid tumors	Phase 1/2
NKTR-262 (Pegylated resiquimod)	✗	Q3W	Intratumoral	✓	✗	Advanced solid tumors with bempegaldesleukin (NKTR-214)	Discontinued Phase 1b/2

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Summary of Investigator Perspective on TransCon IL-2 β/γ and TransCon TLR7/8 Agonist

- Immune checkpoint inhibitors have transformed the management of patients with multiple advanced cancers but have some limitations.
- PD-1/PD-L1 interaction is utilized by cancer but also self-reactive T cells that escape thymic negative selection → unrestrained self-directed autoimmunity and irAEs.
- Primary target cells are antigen-experienced T cells expressing PD-1, with minimal activation of NK cells.
- Effective IO agents are needed beyond checkpoint inhibitors.
- TransCon platform offers ability to transform active drugs into prodrugs with sustained release properties.
- Both TLR agonists and IL-2 therapy have potential to benefit from using TransCon technology.
- Broad development strategy may be needed to explore activity in various indications and with various combination partners or treatment modalities.

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Closing Remarks

TransCon TLR7/8 Agonist Primes Immune Cells Locally for Systemic Antitumor Effect

TransCon TLR7/8 Agonist monotherapy at 0.5mg/lesion IT Q3W, outpatient

- Safety Profile: generally well-tolerated with low systemic side effects
- Long effective half-life with low C_{max}
- Sustained inflammation in the tumor, with high cytokine and chemokine release
- Anti-tumor responses observed in injected and non-injected tumors

Intratumoral TransCon TLR7/8 Agonist uses the injected tumor to elicit systemic anti-tumor effects

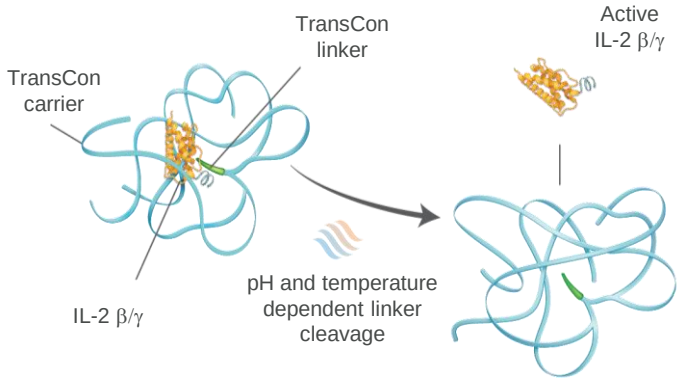
TransCon IL-2 β/γ Provides a Systemic Immune Boost

TransCon IL-2 β/γ monotherapy at 120 μg/kg IV Q3W, outpatient

- Safety Profile: generally well-tolerated with no DLT out of 8 patients dosed; no vascular leak syndrome; no grade 3 or 4 cytokine release syndrome
- Long effective half-life with low C_{max}
- Expands local and systemic cytotoxic immune effector cells (CD8+ T and NK cells) without clear effect on T_{regs} and eosinophils
- Meaningful clinical benefit observed with monotherapy in heavily pre-treated patients

Aiming to cure more cancer patients safely with amplified and durable immune activation

TransCon IL-2 β/γ: Potential Best-in-Class IL-2 Therapy



- **High potency** while preventing binding to IL-2Rα
- **Prodrug design** enables **sustained release** of non-alpha IL-2
- **Selective** expansion of CD8+ T and NK cells without effect on T_{regs} or eosinophils
- **Safety profile** compatible with chronic outpatient administration

	TransCon IL-2 β/γ[1] **5-kDa pegylation, TransCon Technology**	**THOR-707[2]** **30-kDa pegylation**
Recommended Phase 2 Dose (monotherapy)	120 μg/kg Q3W	24 μg/kg Q3W[3]
Retains high potency compared to Aldesleukin	Yes	No
Effective half life	> 35 h	9-12 h
Non-Alpha	Yes	Yes
Expansion of CD8+ T cells median fold change	5.6 (cycle 1, day 8)	4.0 (peak average)
Expansion of NK cells median fold change	20.2 (cycle 1, day 8)	8.4 (peak average)
Meaningful increase of T_{regs} or EOS	No	No
Monotherapy clinical activity at RP2D during dose escalation, indication	1 PR in CRC (n=8 dosed, 3 evaluable as of 28 April, 2023)	1 PR in SCC of unknown primary (n=11)

THOR-707 is repositioned as a once-weekly dosing for 6 weeks and maintained with bi-weekly dosing[3]

Subjective rankings based on publicly available information.
[1]Data on file. [2]Presented at the European Society of Medical Oncology (ESMO) Annual Meeting 2022, September 9–13, 2022. [3]New schedule (QW/Q2W) NCT04009681.
Q3W: every three weeks.

Next Steps for Ascendis' Immunotherapy Program

- Heterogeneity across cancers, organs, and patients requires diversity of approaches to achieve benefit for patients
- TransCon IL-2 β/γ and TransCon TLR7/8 Agonist both showed acceptable safety profile and single-agent clinical activity
- Optimally positioned for combination, with the potential to become a backbone agent in oncology
- Topline/interim analysis from Phase 2 dose expansion cohorts expected in 2024

Using TransCon Platform to develop multi-modal approaches for immune-mediated tumor control

Q&A Session

Email questions to:
IR@ascendispharma.com