ACTIVATING THE PATIENT'S IMMUNE SYSTEM TO FIGHT CANCER

Carnegie Nordic Healthcare

Dr. Erik D Wiklund, CEO

15 March 2022

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OSE: TRVX

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1

Introduction

2. ONCOS-102 intra-tumoral delivery
3. NextGen circRNA ONCOS vectors
4. Summary

THE IMMUNO-ONCOLOGY REVOLUTION

> 500,000 patients treated per year

> 3,000 ongoing clinical trials

> 40% of US cancer patients eligible

> 10 approved products

SOURCE: Research&Markets; Haslam & Prasad 2019, JAMA; Vaddepally et al. 2020, Cancers

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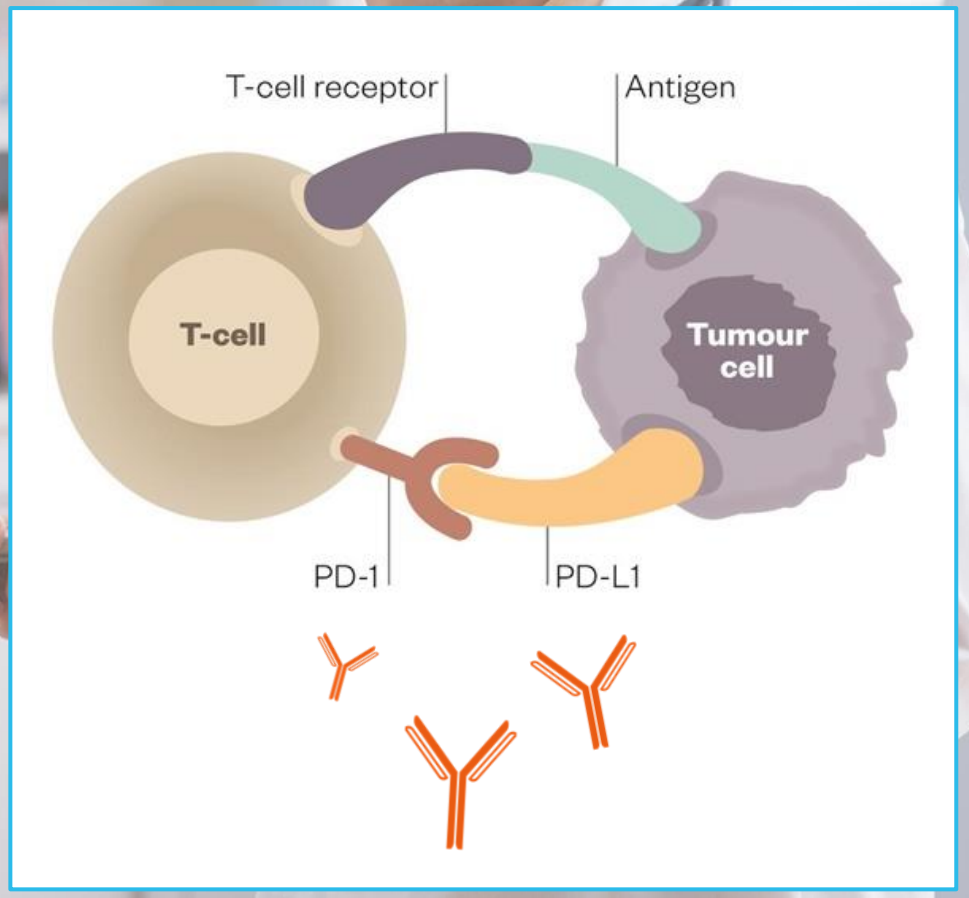
FIRST GENERATION IMMUNO-ONCOLOGY: CHECKPOINT INHIBITORS

Cornerstone of current cancer treatment

Deep and durable responses

$25b annual sales globally

8 products approved to date, many more in development



SOURCE: GlobalData, Research&Markets

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THE CHALLENGE:

MAKE PD1 CHECKPOINT INHIBITORS WORK FOR MORE PATIENTS

0-40% of treated patients respond

>50% of responding patients relapse

1 PD1 checkpoint inhibitor monotherapy not sufficient

SOURCE: Haslam & Prasad, 2019, JAMA

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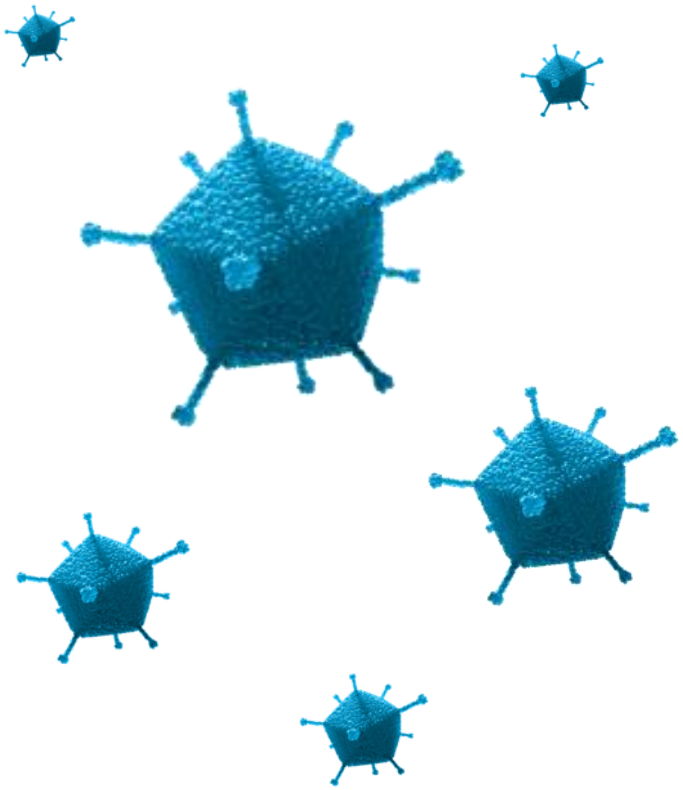
THE SOLUTION: IMMUNE ACTIVATION BY TARGOVAX´S ONCOLYTIC VIROTHERAPY ONCOS



Unblinds the tumor to the immune system

Primes the patient´s T-cells to target cancer cells

Reverses immunosuppressive defense mechanisms in the tumor

Delivers immune stimulatory payloads

TARGOVAX IS CENTERED AROUND FOUR CORE IMMUNE ACTIVATOR DEVELOPMENT PROJECTS

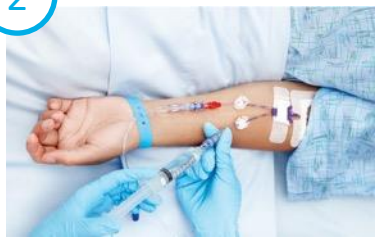
1

ONCOS-102 intra-tumoral delivery

Clinical phase 2

- Efficacy and mechanism-of-action confirmed in multiple settings
- Class-leading data in PD1 refractory melanoma

2

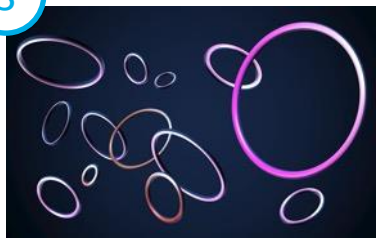


ONCOS-102 systemic delivery

Pre-clinical in vitro / in vivo

- Technology evaluation to enable virus “stealthing” in circulation ongoing
- Broaden opportunity to deep / metastatic tumors

3



ONCOS circRNA delivery platform

Discovery / in vitro PoC

- Build ONCOS vector platform for circRNA delivery
- Develop multi-functional vectors with coding and non-coding payloads

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mutant KRAS immunotherapy

Clinical phase 1

- Clinical stage polyvalent mutKRAS vaccine
- Exploring novel KRAS IO concepts

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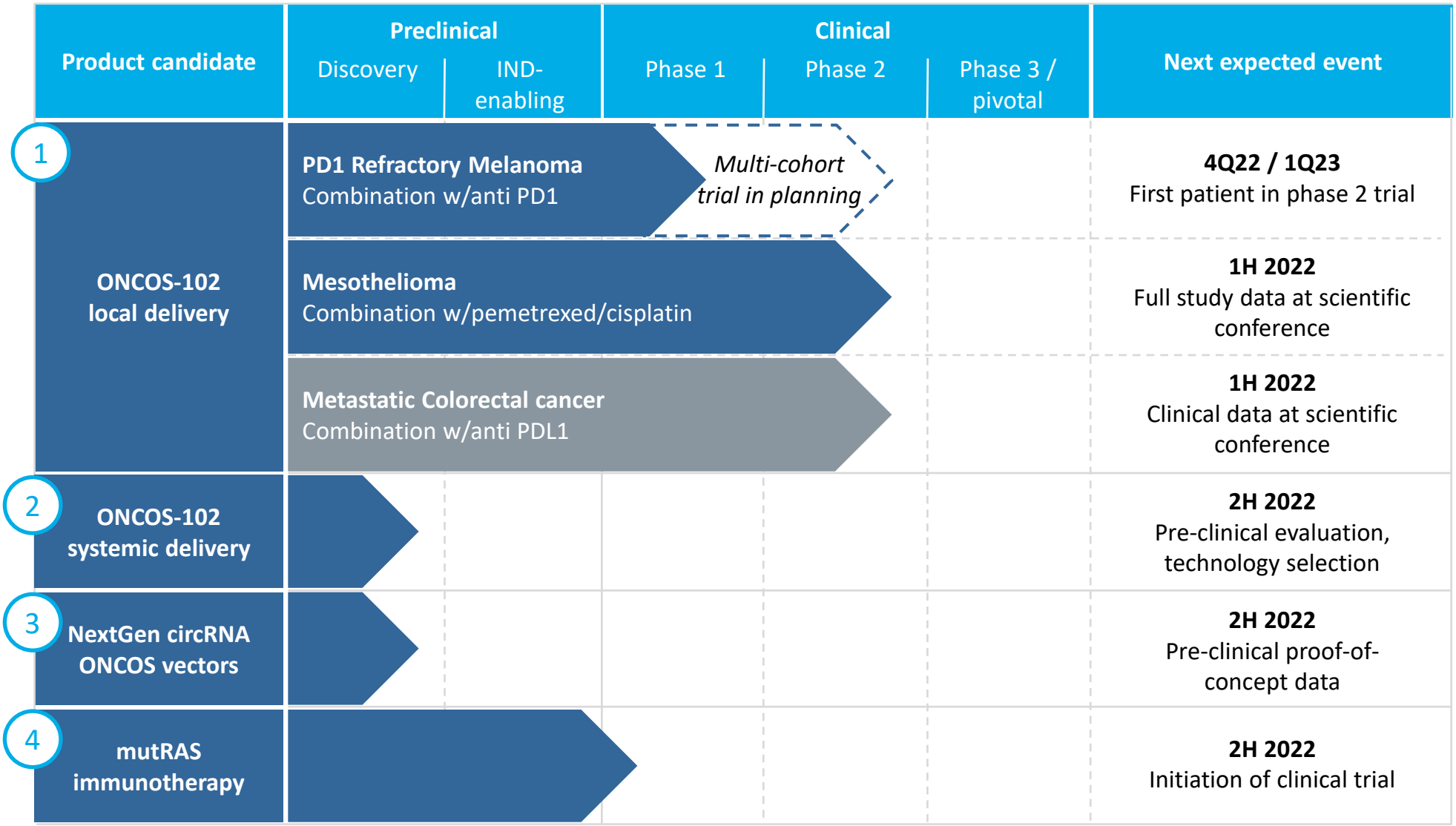
TARGOVAX DEVELOPMENT PIPELINE



Trial run by collaboration consortium

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2

ONCOS-102 intra-tumoral delivery

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TARGOVAX DEVELOPMENT PIPELINE

Product candidate	Preclinical		Clinical			Next expected event
	Discovery	IND-enabling	Phase 1	Phase 2	Phase 3 / pivotal	
1 **ONCOS-102 local delivery**	**PD1 Refractory Melanoma** Combination w/anti PD1		*Multi-cohort trial in planning*			**4Q22 / 1Q23** First patient in phase 2 trial
	Mesothelioma Combination w/pemetrexed/cisplatin					**1H 2022** Full study data at scientific conference
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NextGen circRNA ONCOS vectors						**2H 2022** Pre-clinical proof-of-concept data
mutRAS immunotherapy						**2H 2022** Initiation of clinical trial

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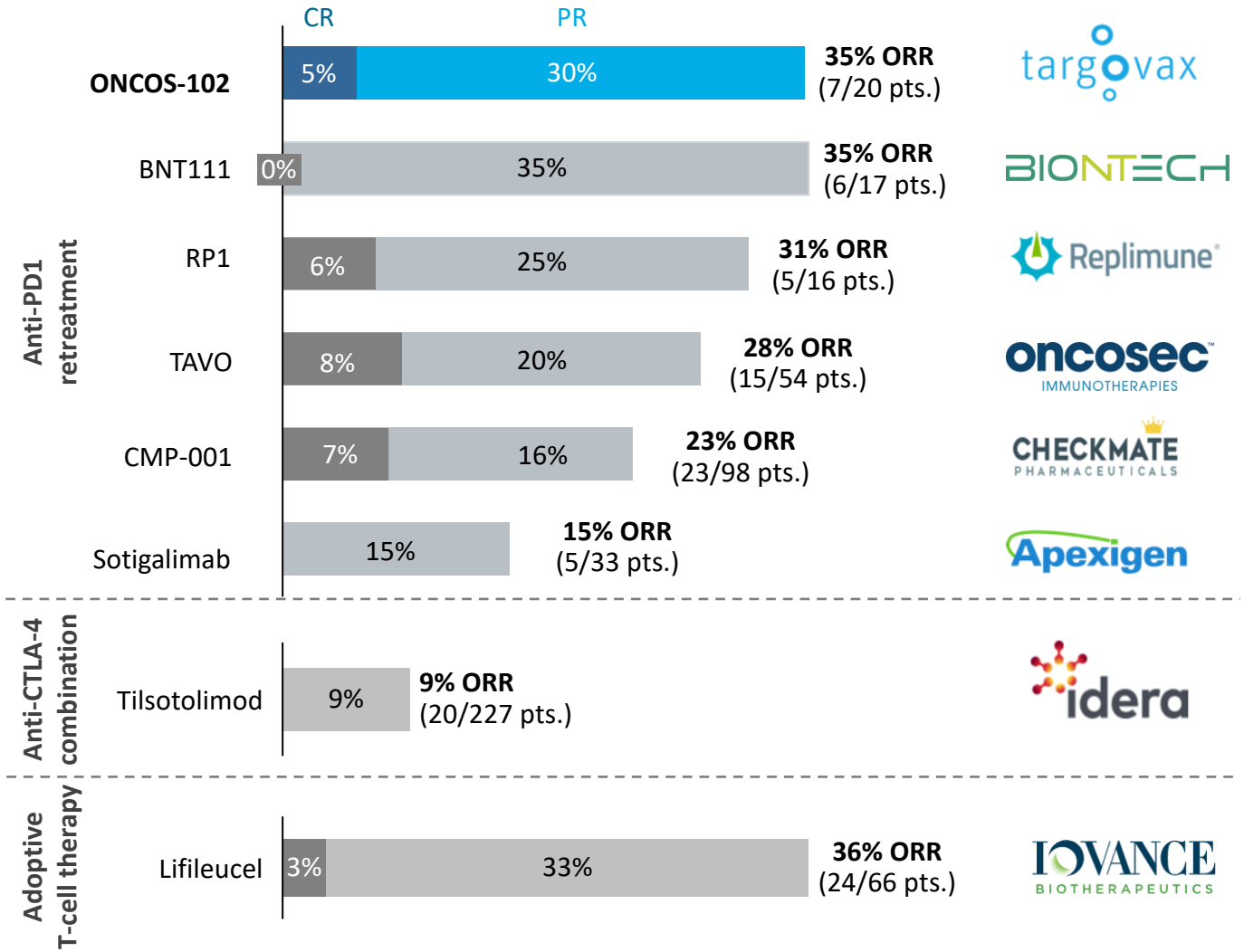
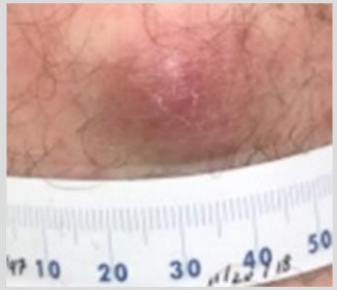
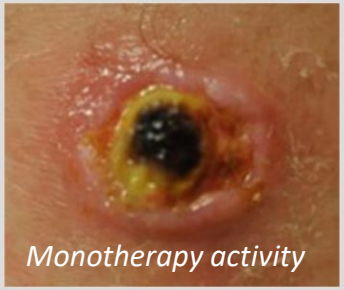
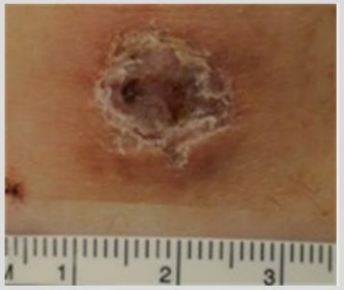
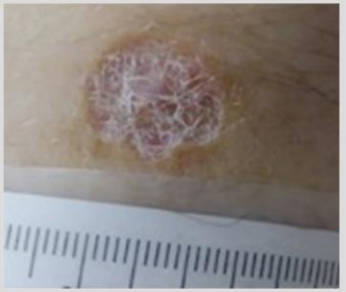
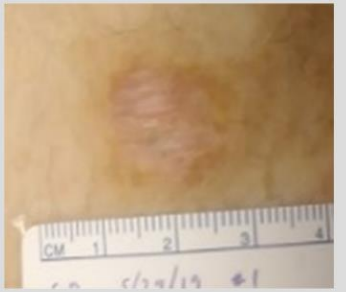
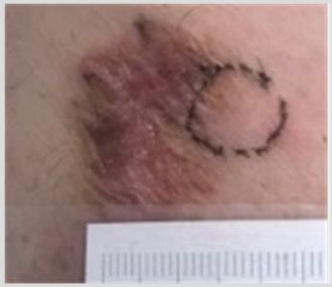
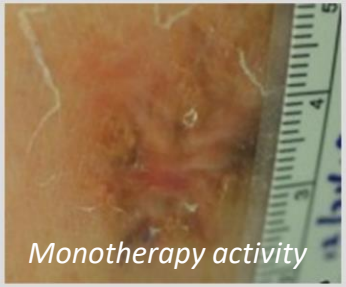
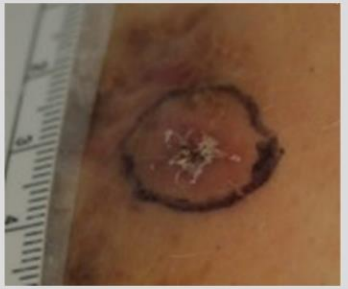
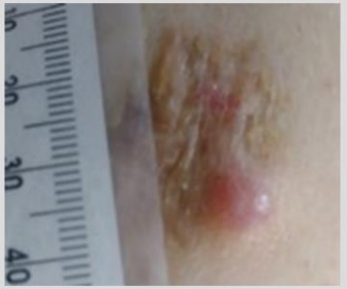
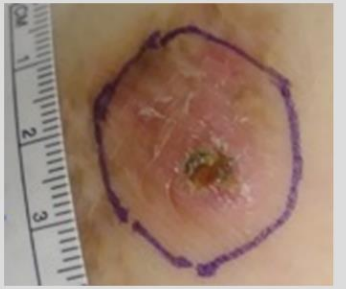
CLASS LEADING ORR OF 35% SHOWN IN PD1 REFRACTORY MELANOMA PHASE 1 STUDY



Targovax market analysis, November 2021

CASE EXAMPLE: PARTIAL RESPONSE IN PATIENT REFRACTORY TO BOTH T-VEC AND ANTI-PD1

Tumor response, 2 of 2 injected lesions

	Baseline	*Week 3*	*Week 9*	*Week 18*	*Week 27 (EoS)*
Lesion 1 of 2					
Lesion 2 of 2					
	Progression on pembrolizumab	3x ONCOS-102 (no pembrolizumab)	3x ONCOS-102 & 2x pembrolizumab	3x ONCOS-102 & 5x pembrolizumab	3x ONCOS-102 & 8x pembrolizumab

Patient characteristics

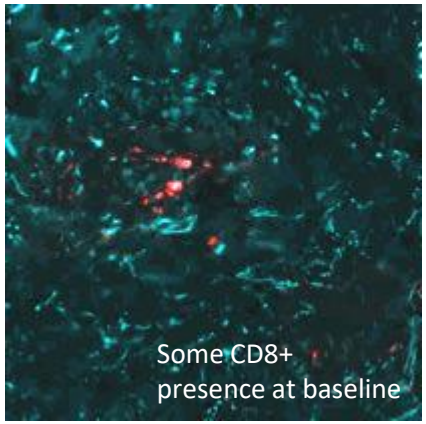
Tumor stage at enrolment:	**IV** T4a, N1b, M1	**Prior therapies:**	Surgery Talimogene-laherparepvec (T-vec) Ipilimumab Pembrolizumab
RECIST 1.1:	**PR**, week 9-27		

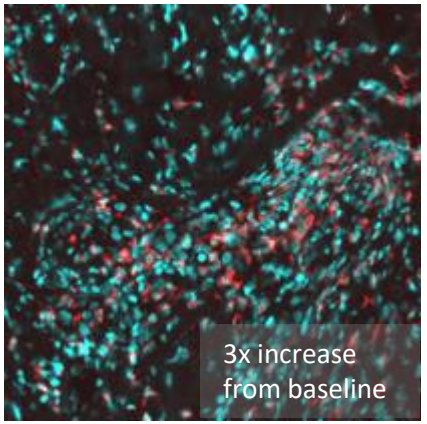
CASE EXAMPLE: PARTIAL RESPONSE PATIENT REFRACTORY TO T-VEC - T-CELL INFILTRATION

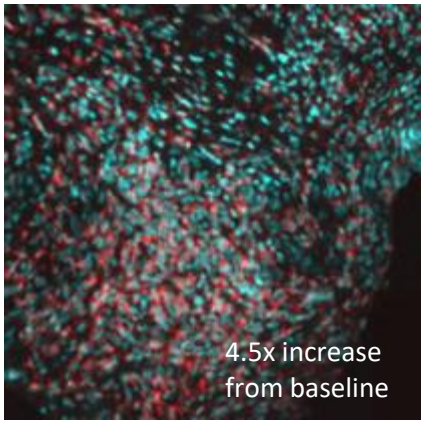
T-cell infiltrate, 1 of 2 injected lesions

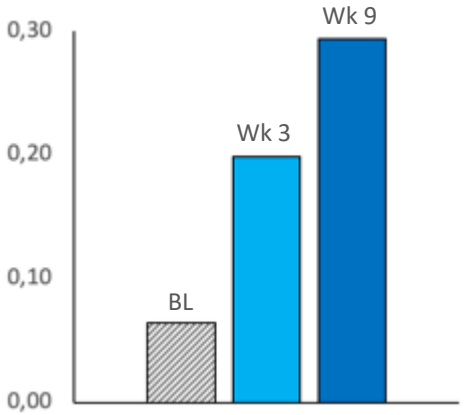
Baseline	*Week 3*	*Week 9*	*Total level of T-cells*

CD8+ T-cells

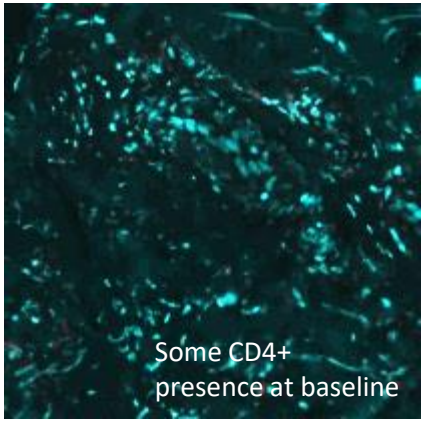


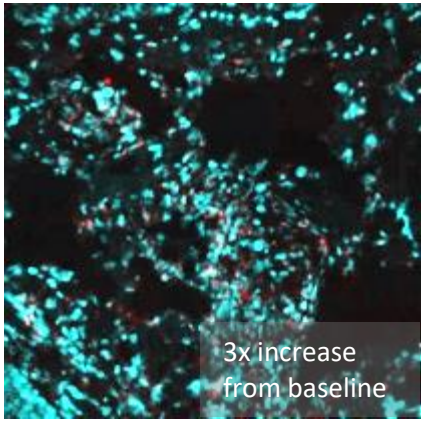


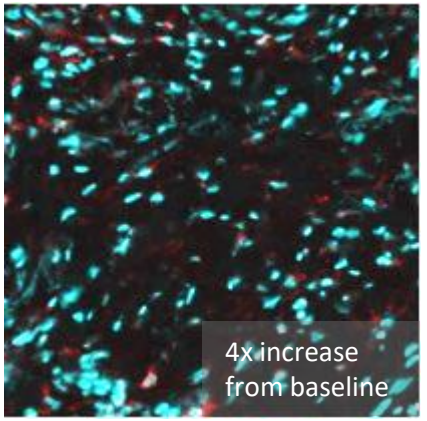


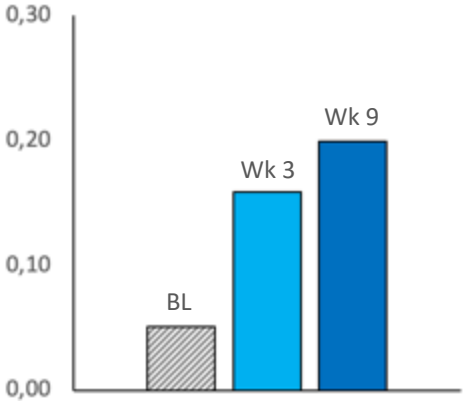


CD4+ T-cells*









Progression on pembrolizumab

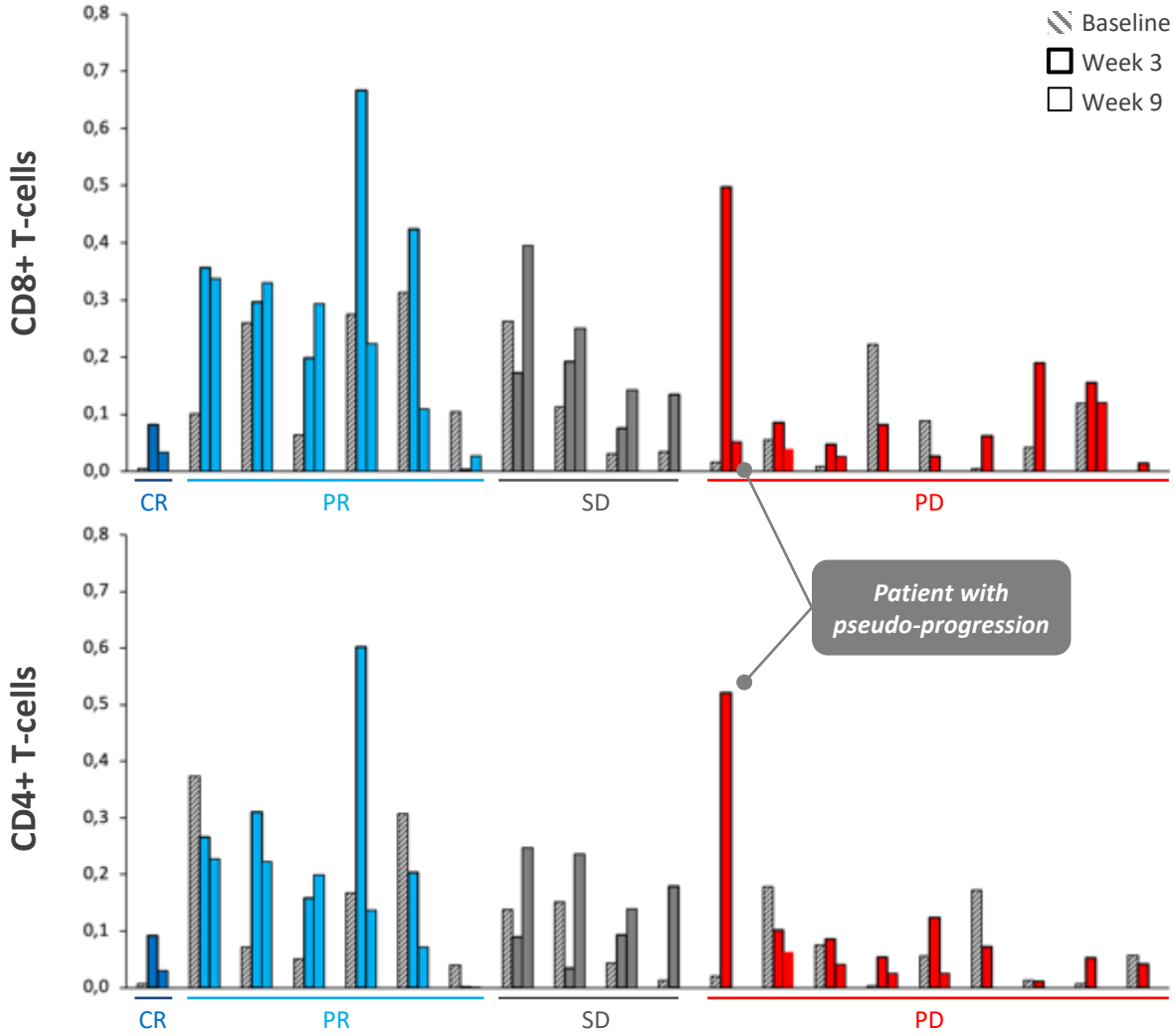
3x ONCOS-102 only

3x ONCOS-102 &
2x pembrolizumab

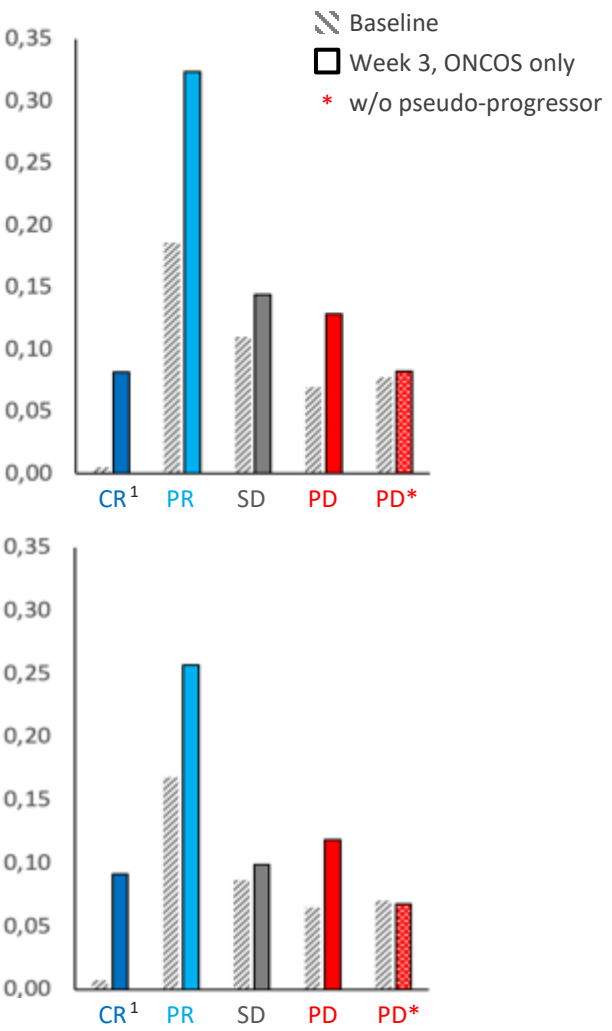
* FOXP3+ cells (T_{reg}) only present at very low level

INCREASED T-CELL INFILTRATION IS CONSISTENT ACROSS PATIENTS, AND ASSOCIATED WITH CLINICAL RESPONSE

T-cell infiltrate (TIL) for individual patients; tumor mIHC, relative level



Average T-cell level per group

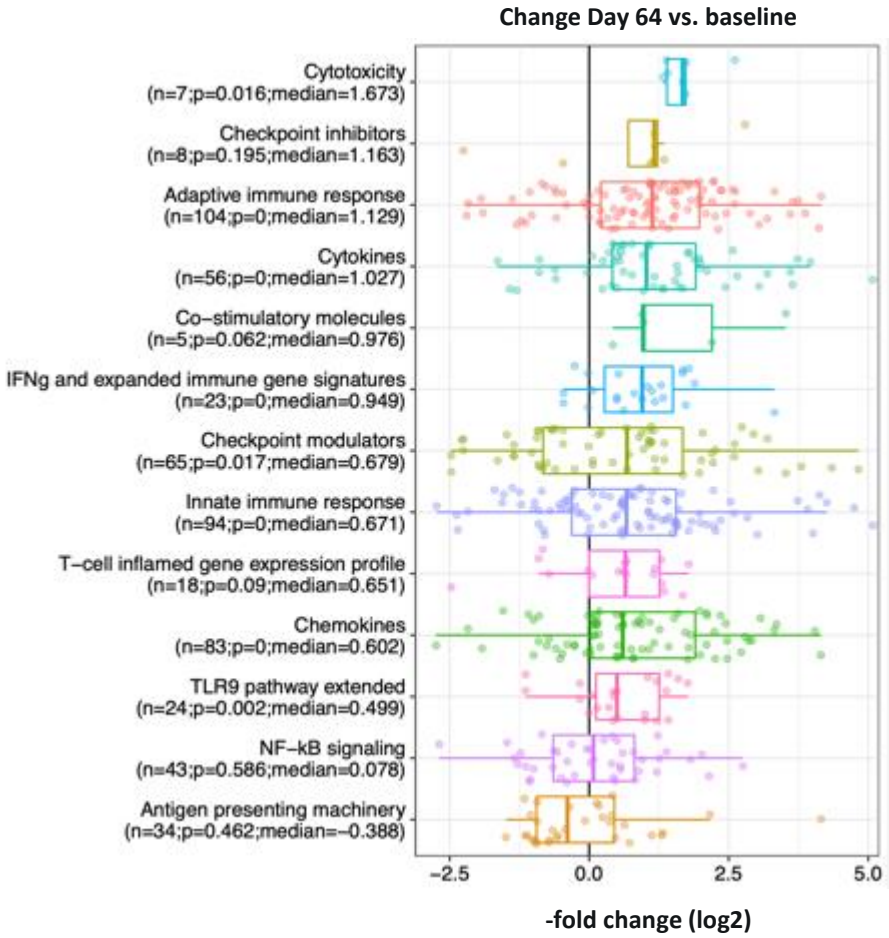


1: One CR patient only

GENE EXPRESSION DATA CONFIRMS IHC OBSERVATIONS AND DETAILS BROAD PRO-INFLAMMATORY TUMOR RE-PROGRAMING

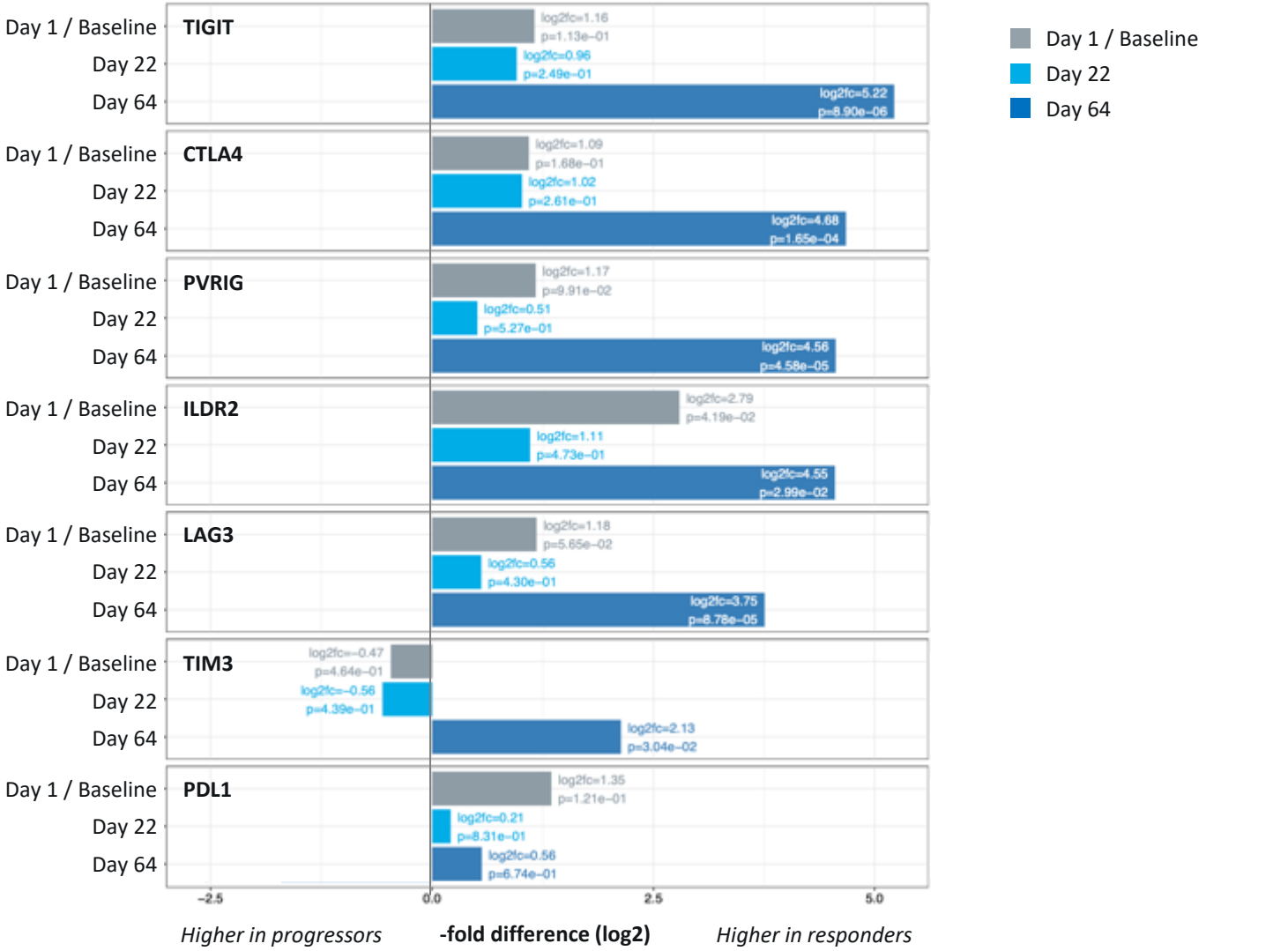
RNAseq gene expression provides further insights:

- **Pro-inflammatory "hot" tumor remodeling** through multiple pathways and molecular mechanisms
- **"Hot" tumor remodeling persists** at least until Day 64, following 6 ONCOS-102 IT administrations and 3 weeks post previous ONCOS-102 injection
- Increased expression of chemokines and cytokines **explain higher immune cell infiltrate**
- Strong upregulation of cytotoxic machinery **explains tumor shrinkage**
- Upregulation of immunomodulatory molecules present **targets for novel combinations beyond anti-PD1**

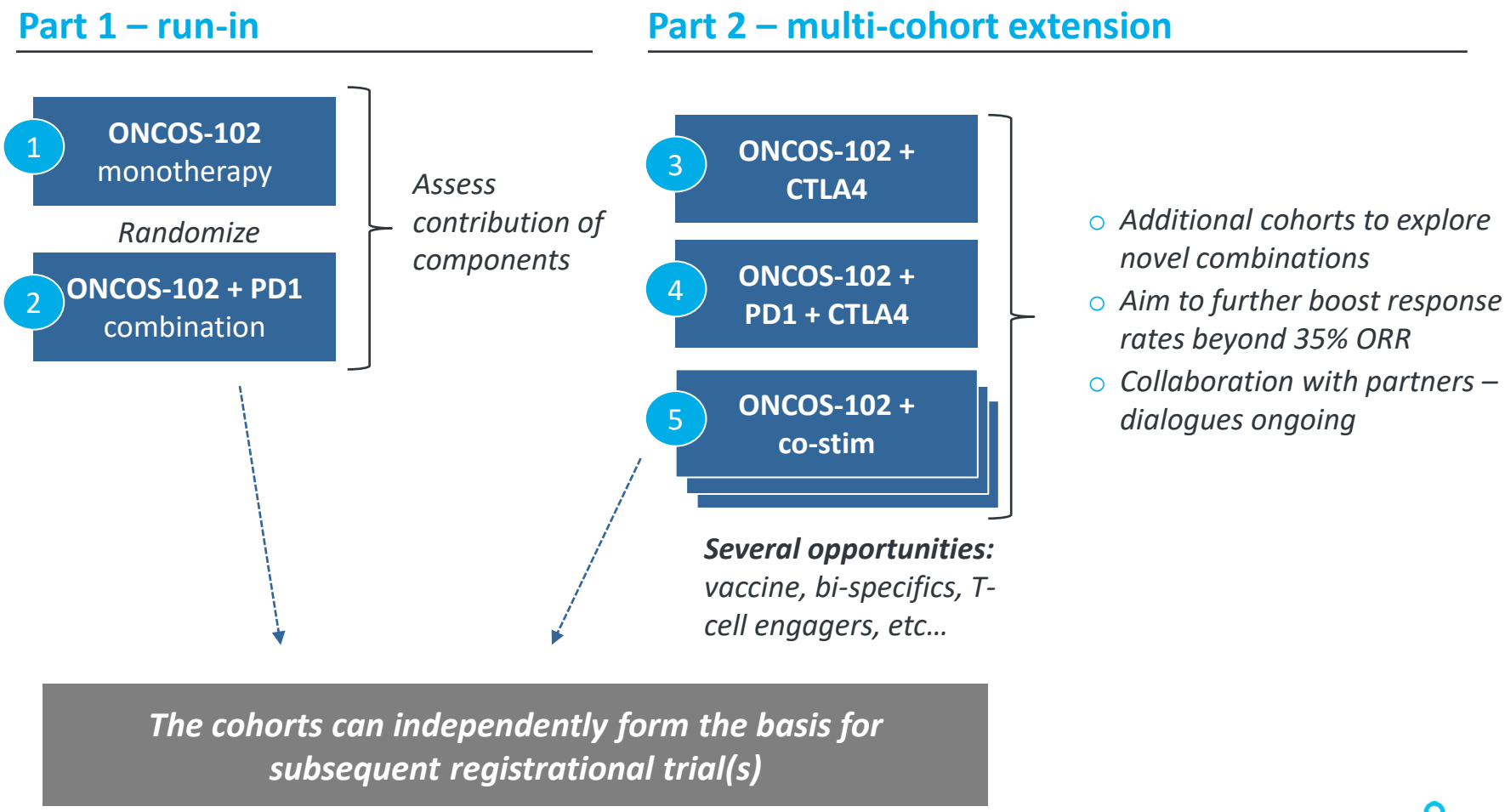


ONCOS-102 DRIVES ROBUST UPREGULATION OF IMMUNE CHECKPOINT INHIBITORS, PARTICULARLY IN RESPONDERS

Expression of immune checkpoint inhibtors, tumor biopsy RNAseq, difference in PR vs. PD patients



NEXT STEP: MULTI-COHORT PHASE 2 TRIAL TO IDENTIFY BEST COMBINATION PARTNER FOR REGISTRATIONAL TRIAL(S)



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TARGOVAX DEVELOPMENT PIPELINE

Product candidate	Preclinical		Clinical			Next expected event
	Discovery	IND-enabling	Phase 1	Phase 2	Phase 3 / pivotal	
	PD1 Refractory Melanoma Combination w/anti PD1		*Multi-cohort trial in planning*			**4Q22 / 1Q23** First patient in phase 2 trial
1 **ONCOS-102 local delivery**	**Mesothelioma** Combination w/pemetrexed/cisplatin					**1H 2022** Full study data at scientific conference
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NextGen circRNA ONCOS vectors						**2H 2022** Pre-clinical proof-of-concept data
mutRAS immunotherapy						**2H 2022** Initiation of clinical trial

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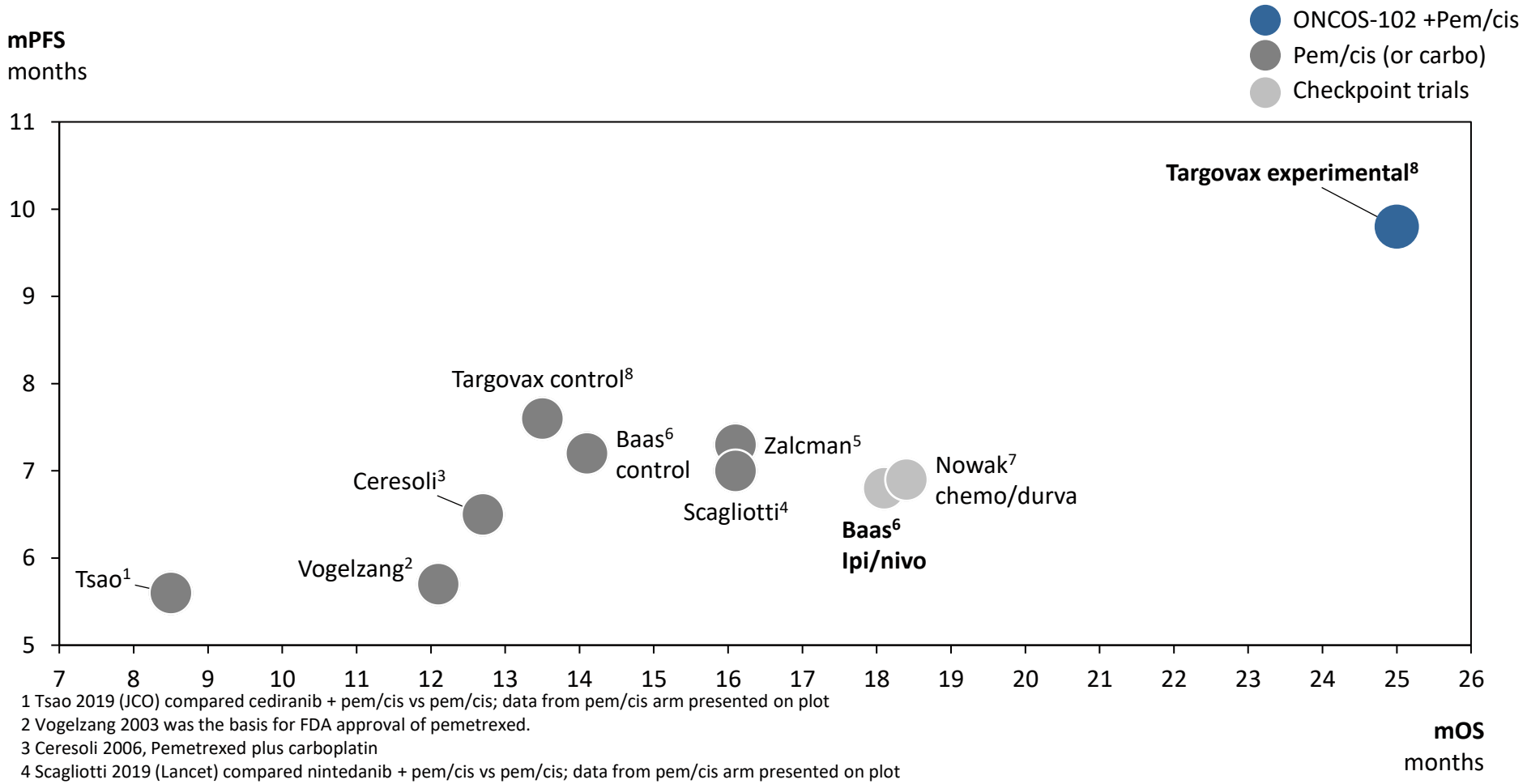
ONCOS-102 HAS SHOWN 25.0 MONTHS mOS IN 1L MESOTHELIOMA, WHICH IS THE BEST SURVIVAL DATA REPORTED IN THIS POPULATION

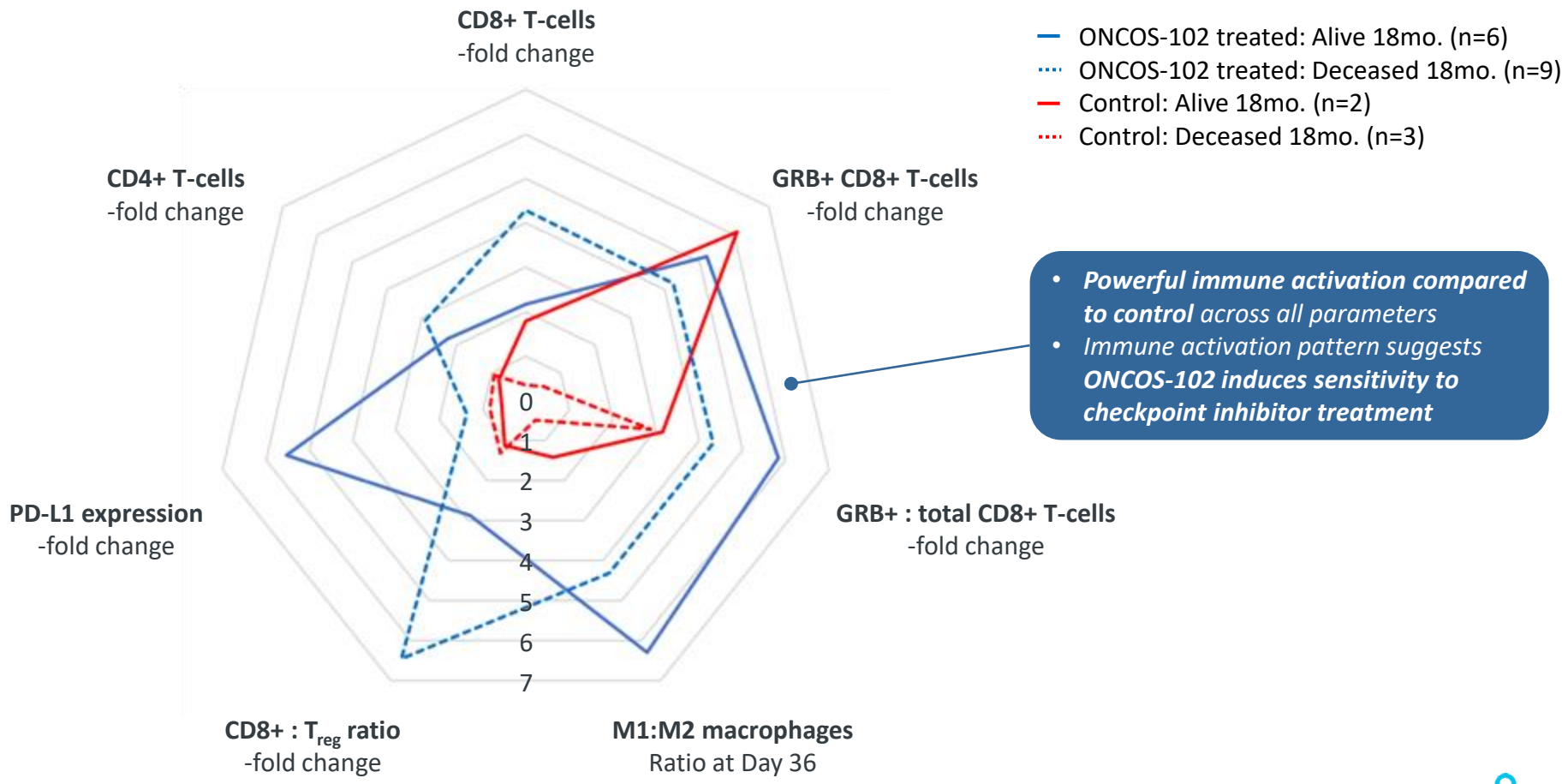


1 Tsao 2019 (JCO) compared cediranib + pem/cis vs pem/cis; data from pem/cis arm presented on plot
2 Vogelzang 2003 was the basis for FDA approval of pemetrexed.
3 Ceresoli 2006, Pemetrexed plus carboplatin
4 Scagliotti 2019 (Lancet) compared nintedanib + pem/cis vs pem/cis; data from pem/cis arm presented on plot
5 Zalcman 2016 (Lancet) compared bevacizumab + pem/cis vs pem/cis; data from pem/cis arm presented on plot.
6 Baas 2021 (The Lancet) CheckMate 743. Nivolumab + ipilimumab for two years vs pem/cis (or carboplatin). Ipi/nivo was approved in first line by FDA on October 2, 2020.
7 Nowak 2020 (Lancet Oncology) Pem / cis (6 cycles) + durvalumab (12 months)
8 1L randomized patients mOS not final: Experimental group, 8 patients (3 censored). Control group, 6 patients (0 censored)

mOS: median Overall Survival. mPFS: median Progression Free Survival

IMPROVED SURVIVAL OUTCOME IS ASSOCIATED WITH POWERFUL ONCOS-102 INDUCED IMMUNE ACTIVATION

Immuno-modulation in tumor tissue; mIHC, Day 36 vs. baseline



- ***Powerful immune activation compared to control*** *across all parameters*
- *Immune activation pattern suggests* ***ONCOS-102 induces sensitivity to checkpoint inhibitor treatment***

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INTRA-TUMORAL ONCOS-102: A CLINICALLY VALIDATED ONCOLYTIC IMMUNE ACTIVATOR

Tested in several treatment **refractory** and immunologically **cold** solid tumors

Treatment-resistant patients

Demonstrated ability both to **shrink tumors** and improve **survival** outcomes

Clinical activity

Drives inflammatory response and **immunological remodelling**, associated with clinical outcome

Validated mode-of-action

Phase 2 multi-cohort trial in aPD1-refractory melanoma building on deep translational insights to launch in 2022

Novel combinations to enhance efficacy

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3

NextGen circRNA ONCOS vectors

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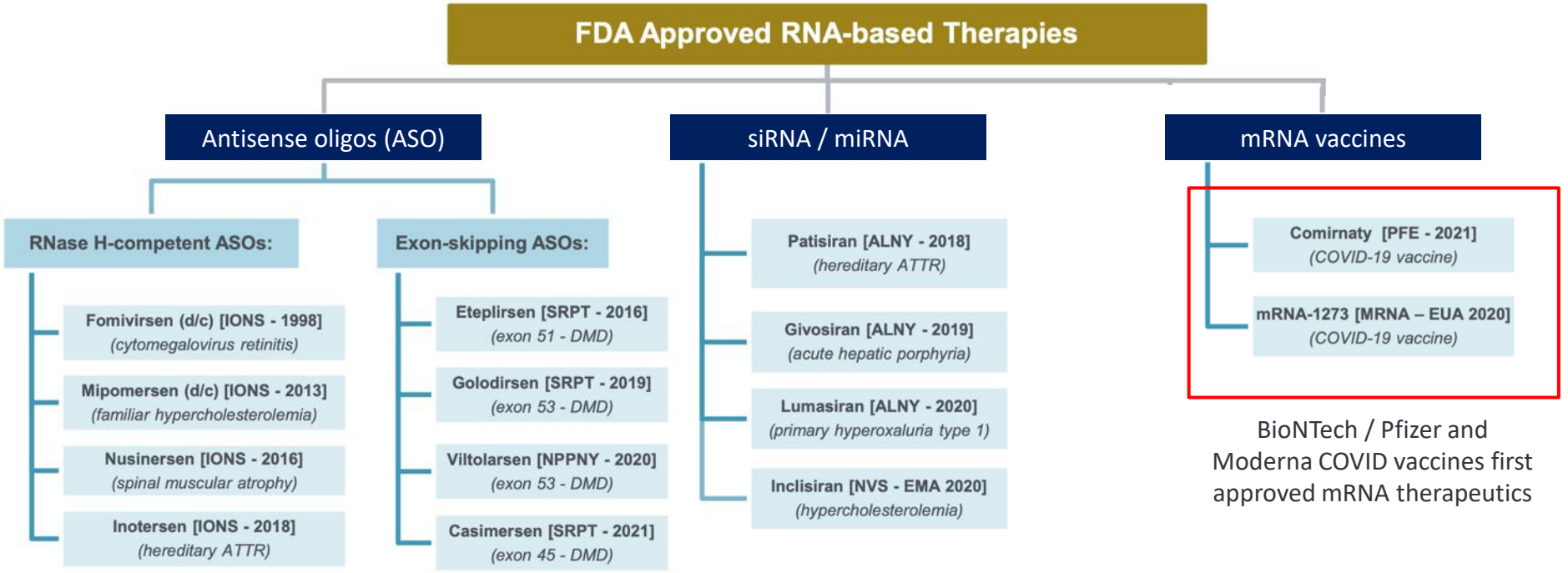
RNA: EMERGING THERAPEUTIC CLASS, DRIVEN BY STRONG RECENT SUCCESS IN COVID VACCINES



BioNTech / Pfizer and Moderna COVID vaccines first approved mRNA therapeutics

No circRNA therapeutic candidates are approved or in clinical stage development

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RNA-BASED THERAPEUTCIS FACE SEVERAL CHALLENGES

Challenges for RNA-based therapies

RNA is chemically unstable

Efficient delivery of RNA drugs remains a major obstacle

Challenging to achieve sufficient spread and penetration into tumors

ONCOS solves these issues through a clinically validated DNA based delivery system that ensures local RNA expression and persistence in the tumor micro-environment

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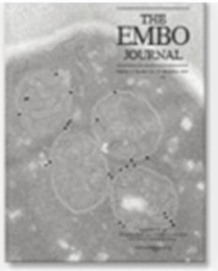
RNA EXISTS NATURALLY IN CIRCULAR FORM AND CAN BE ENGINEERED FOR PROTEIN TRANSLATION

Article | 30 September 2011 | FREE ACCESS

miRNA-dependent gene silencing involving Ago2-mediated cleavage of a circular antisense RNA

Thomas B Hansen,Erik D Wiklund,Jesper B B
Jørgen Kjems



About the cover

Volume 30
Issue 21
2 November 2011

IN THIS ISSUE

768 citations

circRNA discoverers are in the Targovax team

Thomas B. Hansen

Erik D. Wiklund

nature

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nature > letters > article

Published: 27 February 2013

Natural RNA circles function as efficient microRNA sponges

Thomas B. Hansen, Trine I. Jensen, Bettina H. Clausen, Jesp
K. Damgaard & Jørgen Kjems

Nature 495, 384–388 (2013) | Cite this article

95k Accesses | 3825 Citations | 115 Altmetric | Metrics

nature communications

Article | Open Access | Published: 06 July 2018

Engineering circular RNA for potent and stable translation in eukaryotic cells

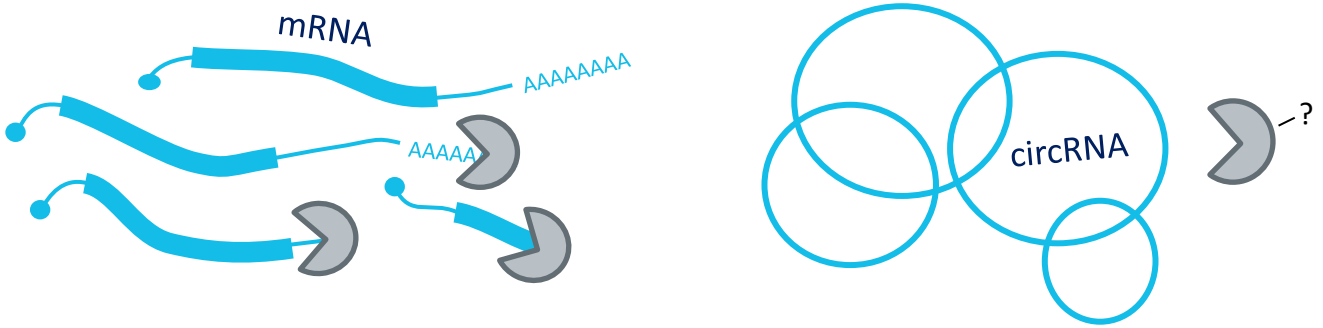
R. Alexander Wesselhoeft, Piotr S. Kowalski & Daniel G. Anderson

CIRCULAR RNA HAVE MULTIPLE ADVANTAGEOUS CHARACTERISTICS AS ANTI-CANCER THERAPEUTICS

Sponging *of oncogenic microRNAs*

Translation for local ***gene therapy***

Circular RNA is resistant to exonuclease degradation



Immunological activation *through pattern recognition receptors (PRR)*

Transcriptional regulation *of target genes*

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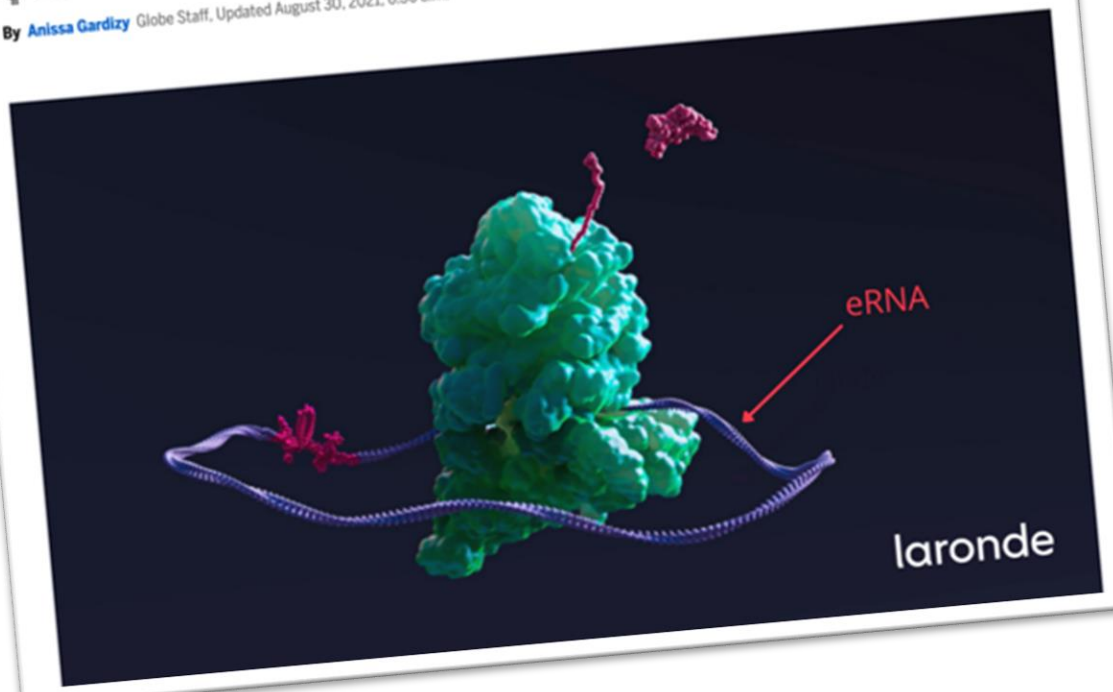
RECENT LAUNCHES OF CIRCULAR RNA GENE THERAPY BIOTECHS HAVE ATTRACTED MEGA SERIES A ROUNDS

As RNA remains hot, Flagship's Laronde raises $440m for a new class of medicines

By Anissa Gardizy Globe Staff, Updated August 30, 2021, 6:30 a.m.



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Orna Therapeutics debuts with $100M, engineered circular RNA treatments to rival cell therapies

nature biotechnology

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News | Published: 02 September 2021

Startups set off new wave of mRNA therapeutics

Elie Dolgin

Nature Biotechnology **39**, 1029–1031 (2021) | Cite this article

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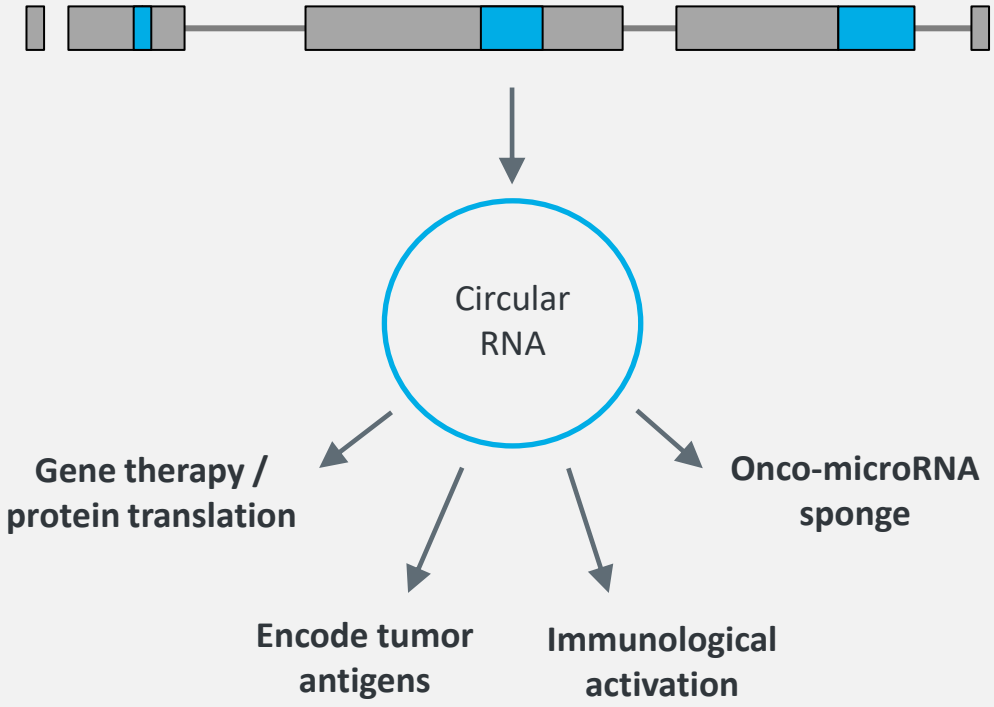
After the vaccine triumphs of Pfizer/BioNTech and Moderna, a raft of startups is developing mRNA, circular RNA and self-amplifying RNA therapeutics.

ONCOS PROVIDES AN IDEAL, CLINICALLY VALIDATED PLATFORM FOR CIRCULAR RNA

Novel ONCOS circRNA vectors



Highly verstaile delivery system

Aims of ONCOS circRNA program:

- Generate ***in vitro*** **proof-of-concept** data package by 2H 2022
- **Build technology platform** IP portfolio and know-how
- Construct **multi-functional novel circONCOS candidates** for in-house development
- **Establish collaborations** to generate circONCOS candidates encoding **partner´s payload of choice**

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4

Summary

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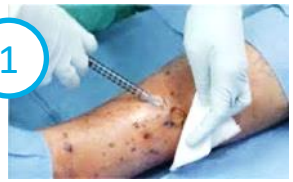
BROADLY POSITIONED FOR FUTURE SUCCESS

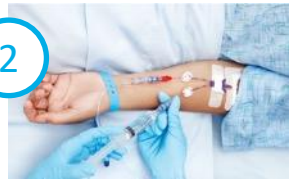
1



Local ONCOS-102 delivery melanoma

- *Class-leading data in PD1-refractory melanoma*

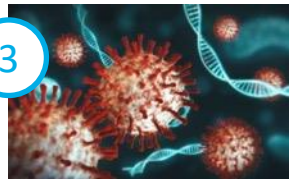
2



ONCOS systemic delivery

- *Expand commercial opportunity through IV delivery*

3



NextGen vectors for circRNA delivery

- *First-in-class circular RNA program driven by world-leading RNA scientists*

4

Mutant KRAS vaccine program

- *Additional opportunity in KRAS mutant cancer through cost-efficient partnership model*

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