ACTIVATING THE PATIENT'S IMMUNE SYSTEM TO FIGHT CANCER

ABGSC Life Sciences Summit

Dr. Erik Digman Wiklund, CEO

19 May 2022

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OSE:
TRVX

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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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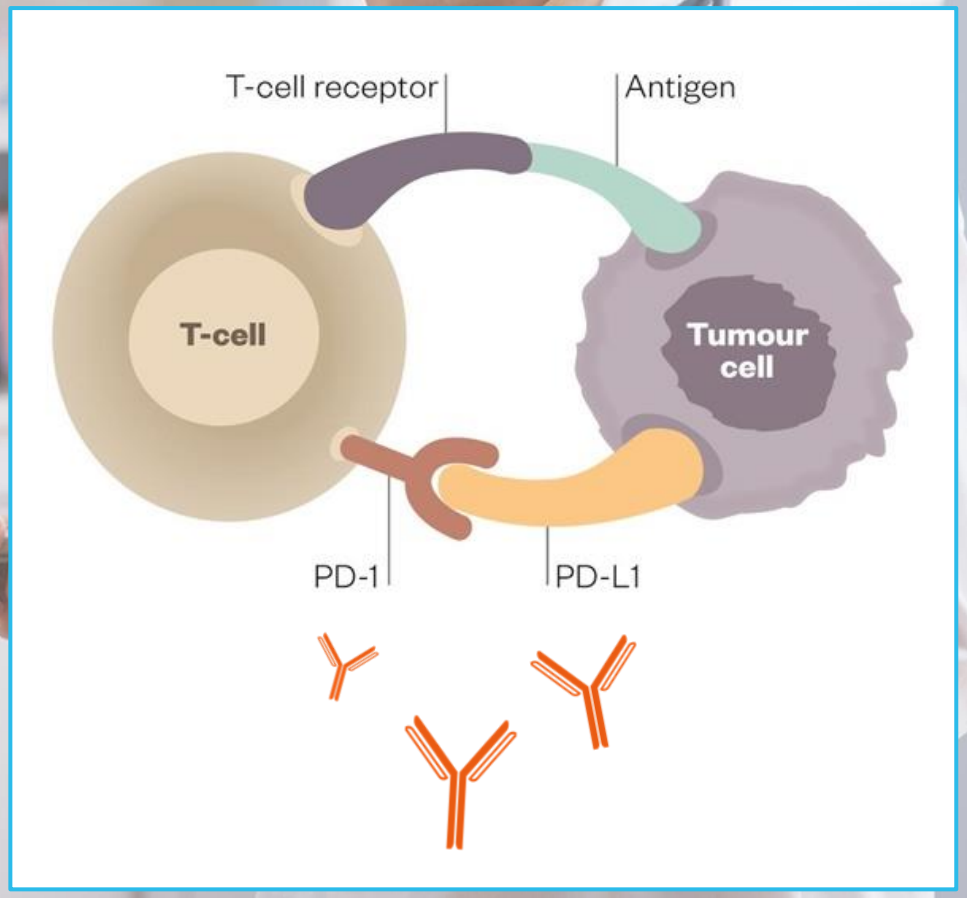
FIRST GENERATION IMMUNO-ONCOLOGY: CHECKPOINT INHIBITORS

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

THE CHALLENGE:

MAKE PD1 CHECKPOINT INHIBITORS WORK FOR MORE PATIENTS

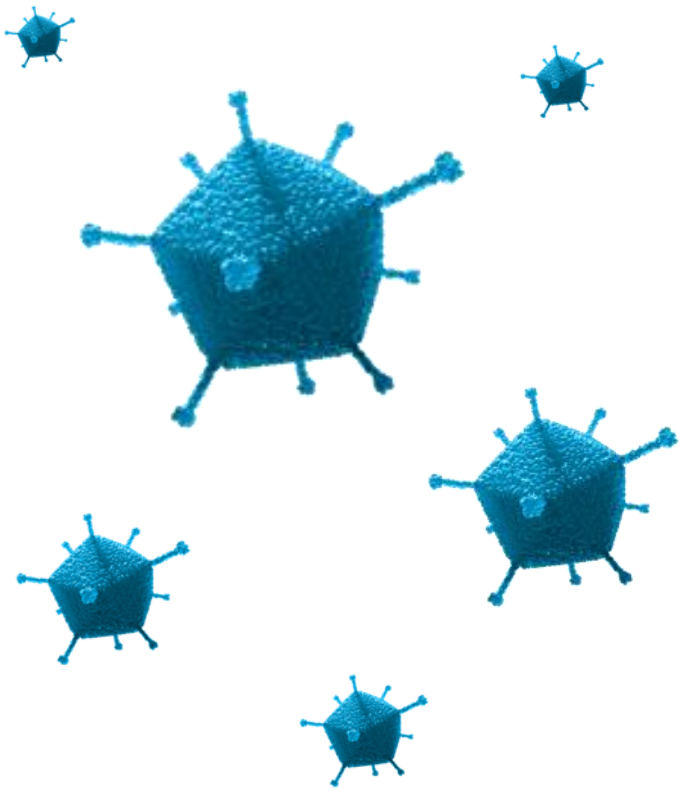
0-40% of treated patients respond

>50% of responding patients relapse

1 PD1 checkpoint inhibitor monotherapy not sufficient

SOURCE: Haslam & Prasad, 2019, JAMA

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



Reverses immuno-suppressive defence mechanisms in the tumor

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

Delivers immune stimulatory payloads

TARGOVAX DEVELOPMENT PIPELINE

Product candidate	Preclinical		Clinical			2022 Milestones
	Discovery	IND-enabling	Phase 1	Phase 2	Phase 3 / pivotal	
ONCOS-102 local delivery	**PD1 Refractory Melanoma** Combination w/anti PD1			*Multi-cohort trial in planning*		**4Q 2022 / 1Q 2023** Initiation of phase 2 trial
	Mesothelioma Combination w/pemetrexed/cisplatin					**1H 2022** Full study data at scientific conference
	Metastatic Colorectal cancer Combination w/anti PDL1					**1H 2022** Clinical data at scientific conference
Mutant KRAS immunotherapy	**Multiple Myeloma TG01 / QS-21**					**2H 2022** Initiation of clinical trial
circular RNA ONCOS vectors						**2H 2022** Pre-clinical proof-of-concept data

Trials run and financed by collaboration partners

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Lead clinical program:

ONCOS-102

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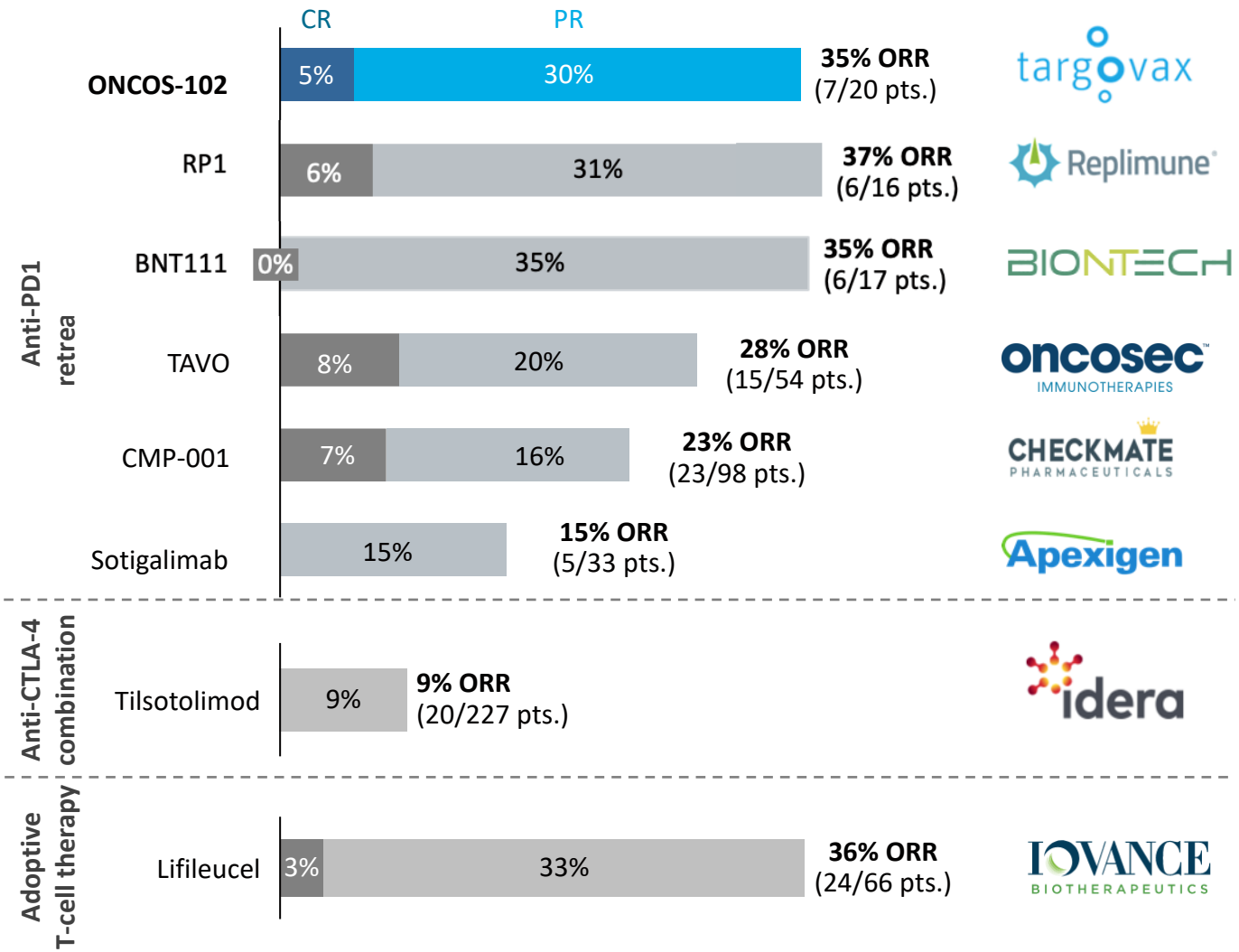
PD1 REFRACTORY MARKET OPPORTUNITY

GROWING UNMET NEED WITH INCREASED ANTI-PD1 USE

Incidence	~100,000 new stage III/IV cases of malignant melanoma per year in the major markets
Unresectable	~50% recur and become unresectable Total ~50,000 patients per year
PD1 resistance	~50% of cases become PD resistant Total **~25,000 patients per year**
Addressable	**Estimated 10,000 – 20,000 patients per year** addressable with intra-tumoral therapies
Other PD1 resistance	**>100,000 patients per year lung cancer** **>50,000 patients per year head and neck**

SOURCE: GlobalData, Targovax analysis

ONCOS-102 HAS DEMONSTRATED HIGHLY COMPETITIVE ORR OF 35% IN PD1 REFRACTORY MELANOMA



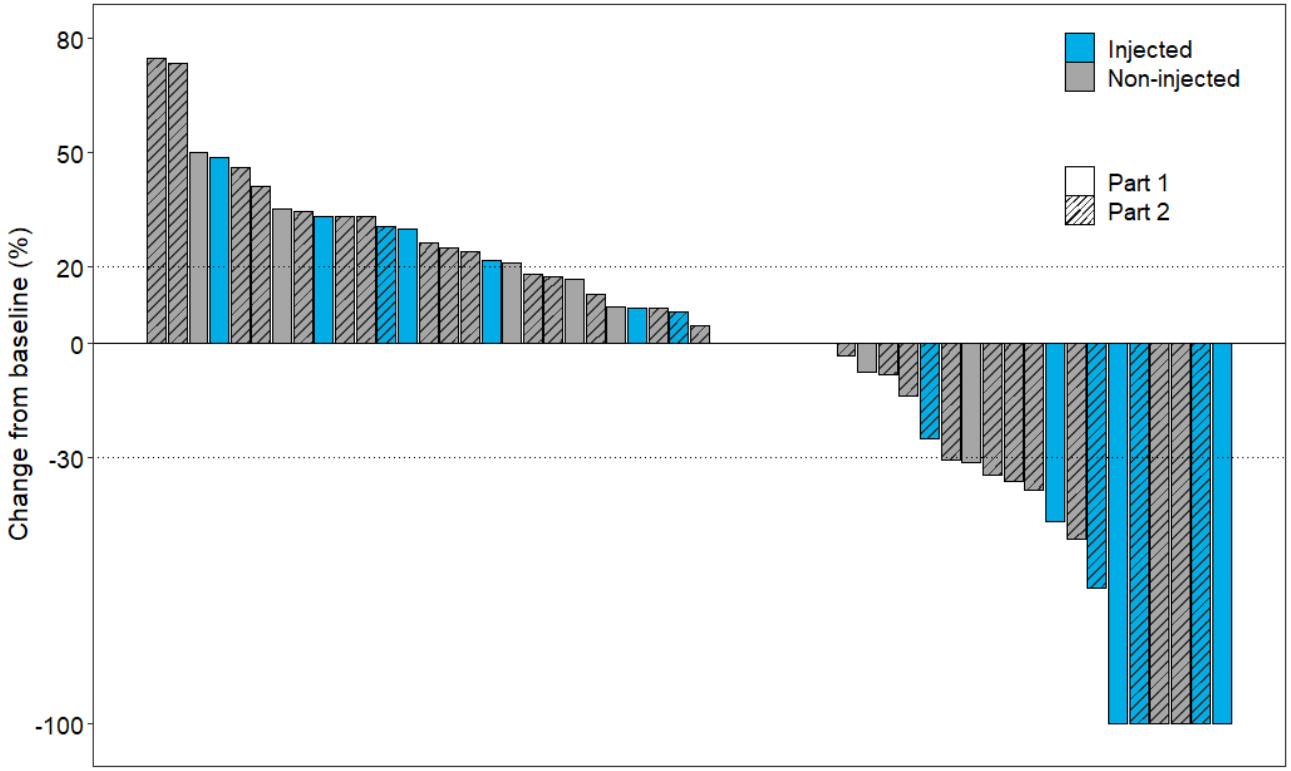
Targovax market analysis, November 2021

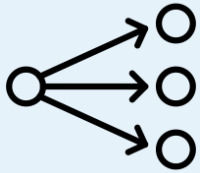
MULTIPLE EXAMPLES OF SYSTEMIC (ABSCOPAL) EFFECT

NON-INJECTED LESIONS COMPLETELY DISAPPEARED IN TWO PATIENTS

Response in individual tumors

% change from baseline; injected and non-injected target lesions





Observed systemic effect:

- **12 of 36 (33%)** non-injected target lesions reduced in size
- **8 of 15 (53%) patients** had reduction in non-injected target lesions
- **4 of 15 patients (27%)** with abscopal Partial Response according to RECIST 1.1 tumor shrinkage criteria

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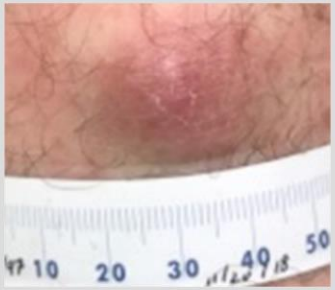
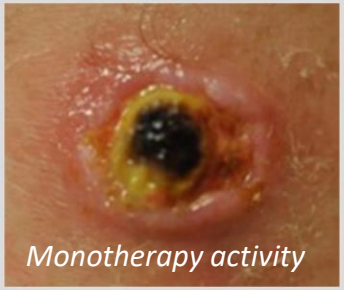
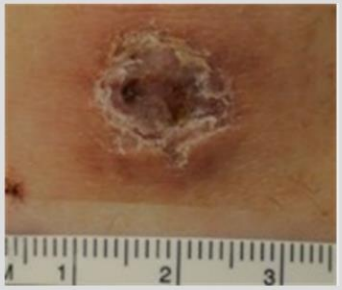
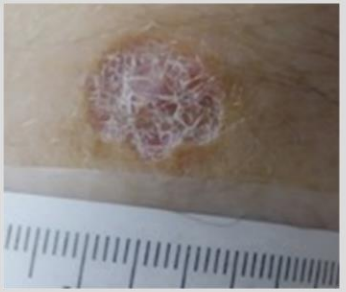
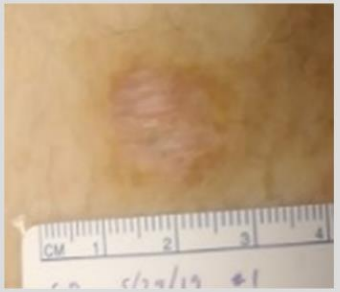
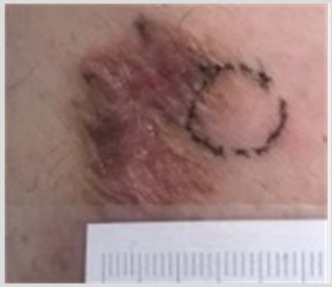
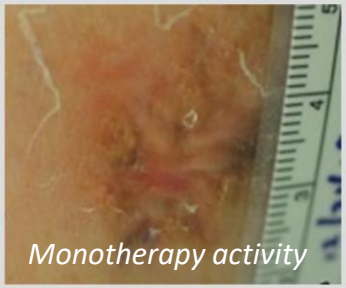
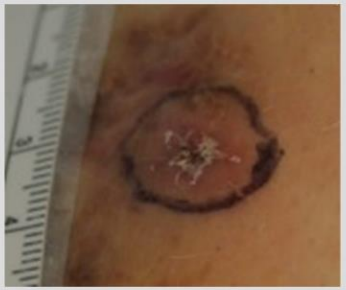
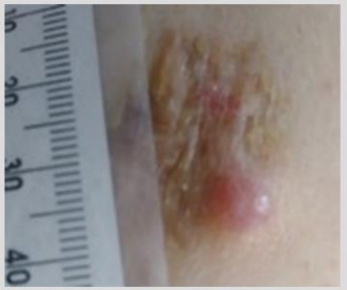
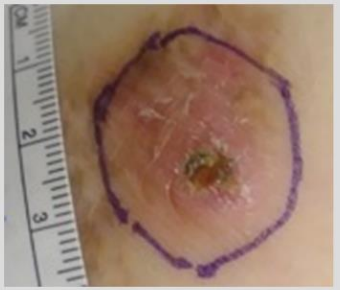
CASE EXAMPLE: PARTIAL RESPONSE IN PATIENT REFRACTORY TO BOTH T-VEC AND ANTI-PD1

Tumor response, 2 of 2 injected lesions

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

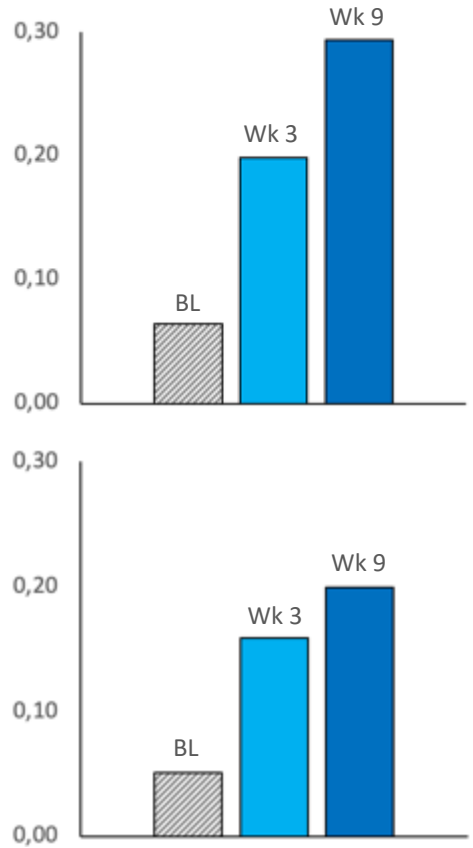
Patient characteristics

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	Some CD8+ presence at baseline	3x increase from baseline	4.5x increase from baseline	
CD4+ T-cells	Some CD4+ presence at baseline	3x increase from baseline	4x increase from baseline	
	Progression on pembrolizumab	3x ONCOS-102 only	3x ONCOS-102 & 2x pembrolizumab	



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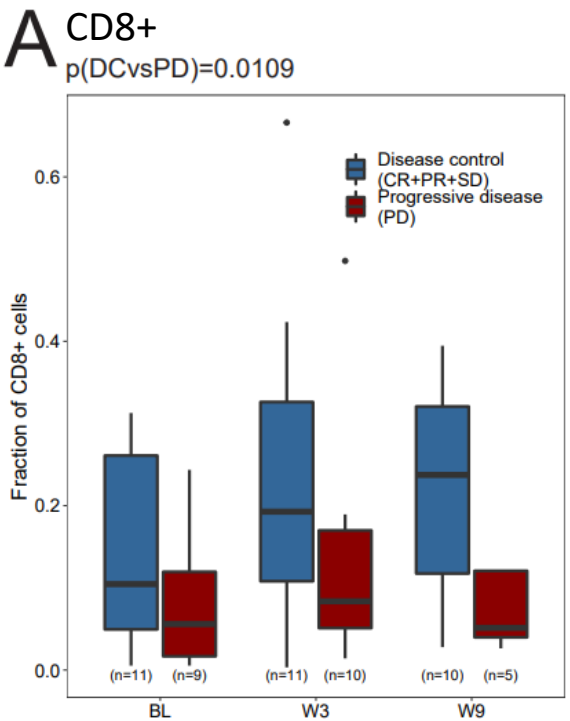
STRONG INCREASE IN INFILTRATION OF T-CELLS IN RESPONDING PATIENTS

Multiplex immunofluorescence – T-cells



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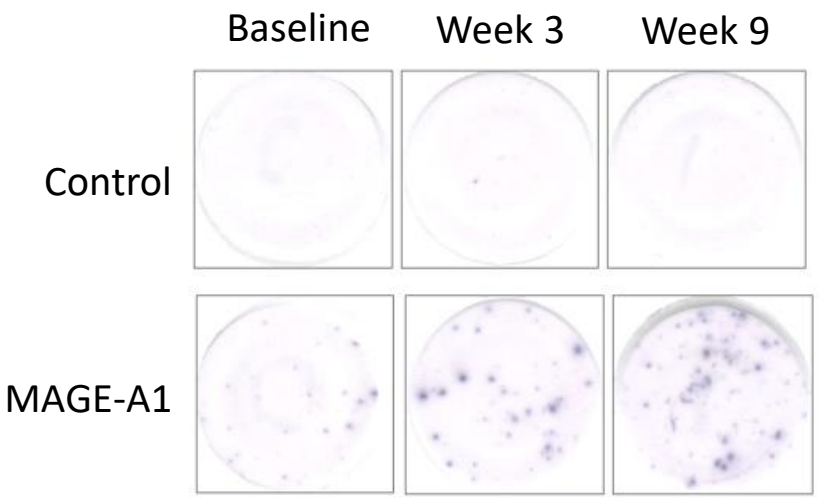
EVIDENCE OF SYSTEMIC TUMOR CONTROL BY ANTIGEN-SPECIFIC T-CELLS

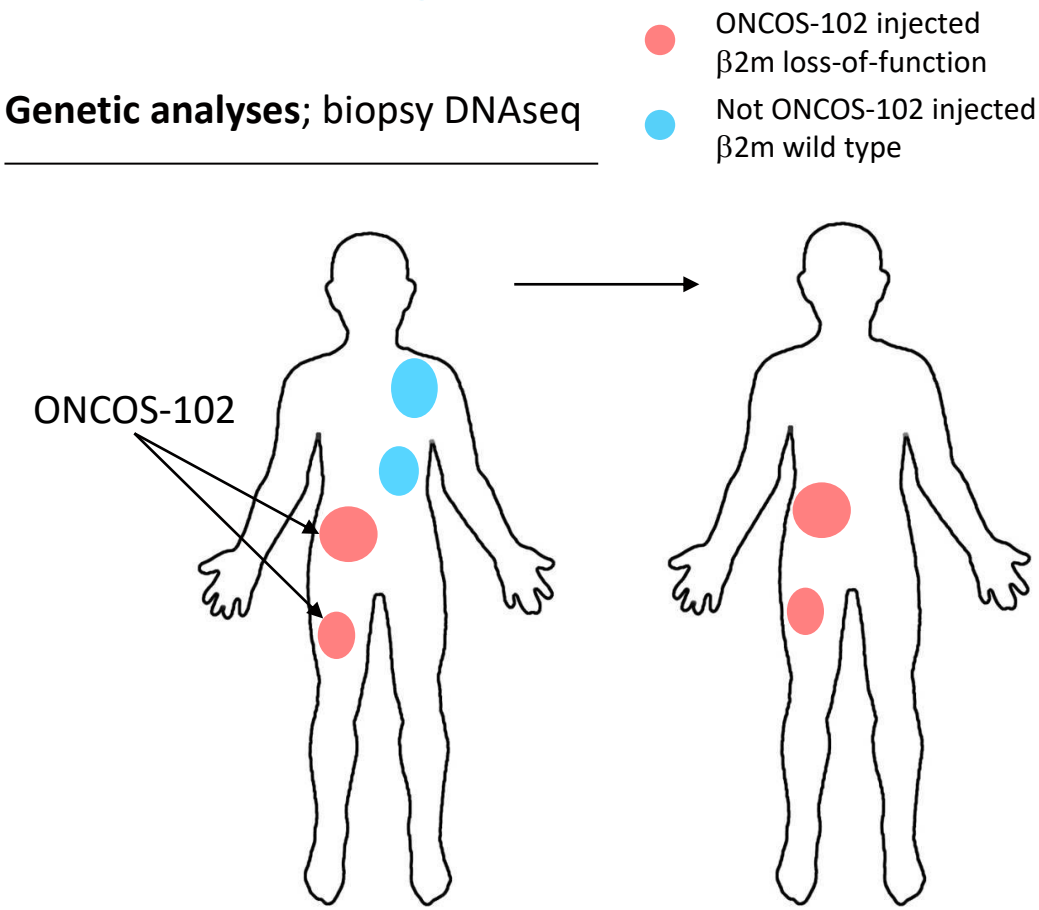
T-cell specificity; PBMC IFNg elispot

Patient w/ complete response



- Sustained tumor antigen-specific T-cell responses observed in several patients by elispot analyses of PBMCs

Genetic analyses; biopsy DNAseq



- β2m-deficiency only observed in progressing patients
- One patient with β2m-deficient injected lesions showed response in non-injected β2m wild type lesions

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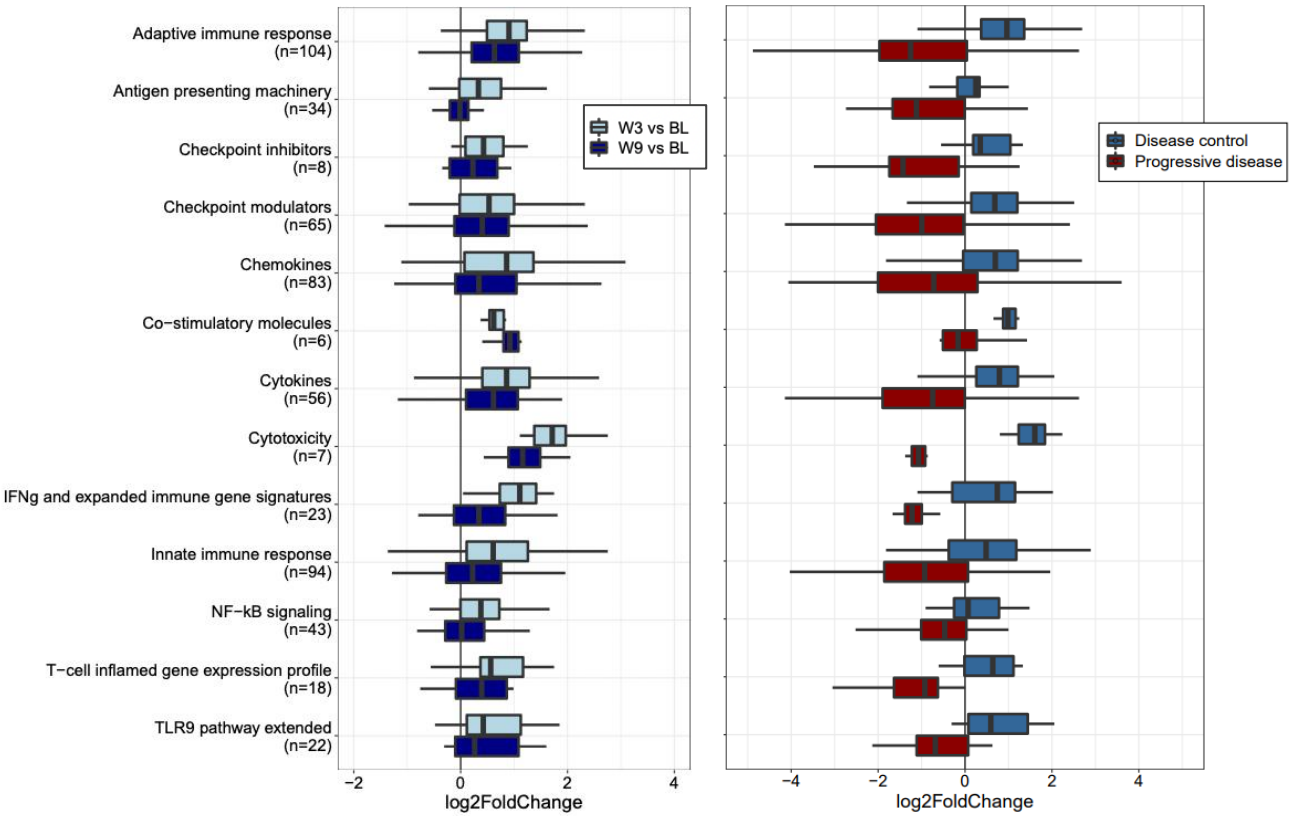
GENE EXPRESSION DATA CONFIRMS IHC OBSERVATIONS AND DETAILS BROAD PRO-INFLAMMATORY TUMOR RE-PROGRAMING

Activation of immune related gene signatures

Week 3 & 9 vs. Baseline | DCR vs. progression



All patients: *Broad activation of immune gene signatures relative to BL*

Responders vs. non-responders: *Immune gene activation only persists in responders at week 9*

RNAseq gene expression insights:

- **Pro-inflammatory "hot" tumor remodeling** by multiple pathways
- **"Hot" tumor remodeling persists at least until week 9,** following 6 ONCOS-102 injections
- Immune gene activation **strongest and most persistent in responders**
- Strong activation of **cytotoxicity** and increased expression of **chemokines and cytokines**

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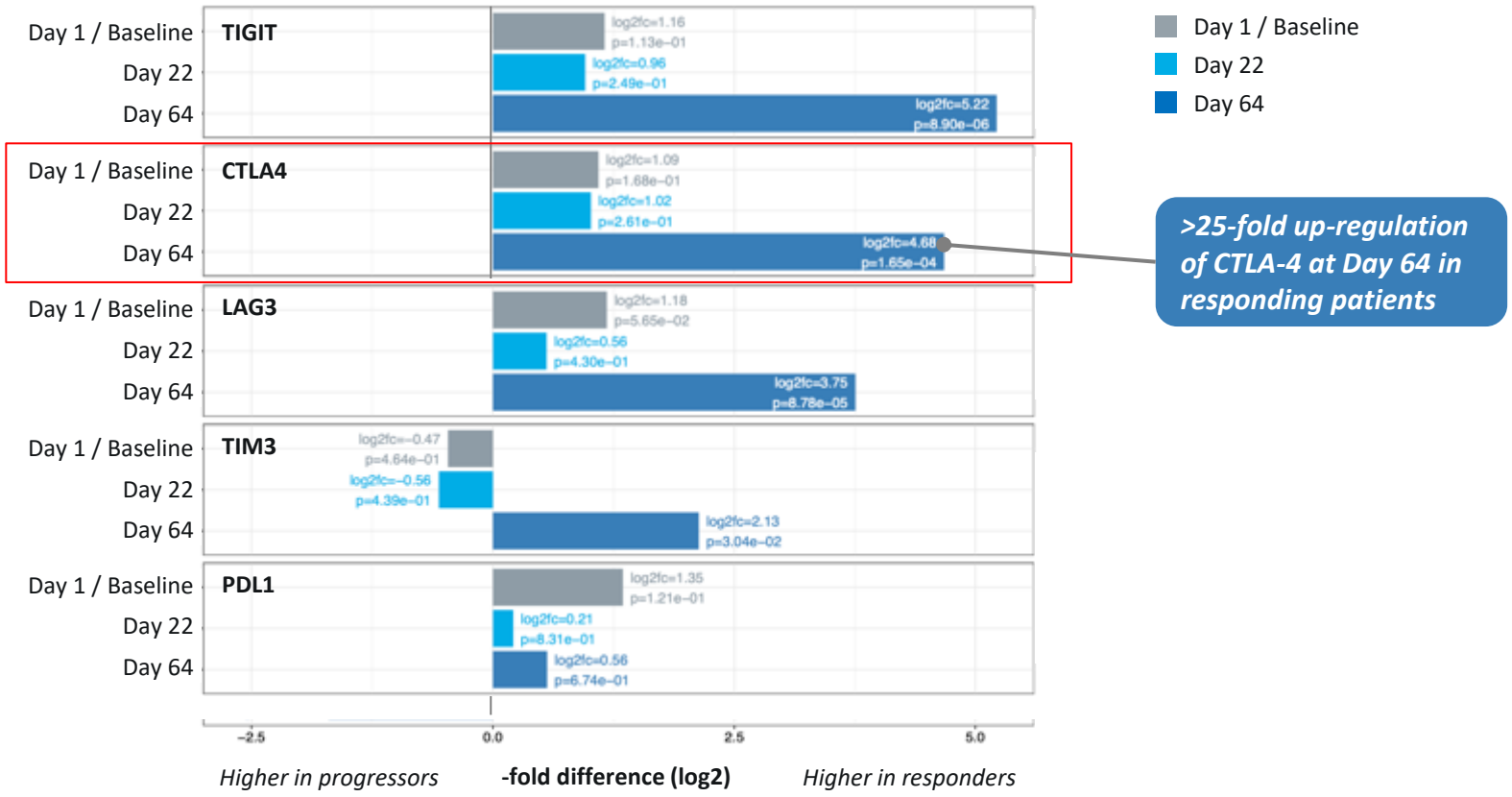
CTLA-4 IS STRONGLY UPREGULATED IN RESPONSE TO ONCOS-102 IN MELANOMA

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



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STRONG RATIONALE FOR COMBINING ONCOS-102 WITH A CTLA-4 CHECKPOINT INHIBITOR

Reverse immuno-suppression

CTLA-4 blockade depletes inhibitory regulatory T-cells both within the tumor and systemically

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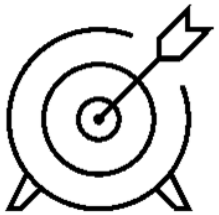

Enhance anti-tumor T-cell priming

CTLA-4 blockade enhances the priming of tumor-specific cytotoxic T-cells

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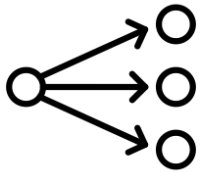

Boost systemic activity

Enhanced tumor-specific T-cell priming leads to better systemic effect

NEXT STEP: MULTI-COHORT PHASE 2 TRIAL TO INCLUDE ONCOS-102 + ANTI-CTLA-4 COMBINATION

Part 1 – run-in

1. **ONCOS-102** monotherapy

Randomize

2. **ONCOS-102 + balstilimab**

Assess contribution of components, confirm dose

Part 2 – multi-cohort extension

3. **ONCOS-102 + botensilimab**
4. **ONCOS-102 + balstilimab + botensilimab**
5. **ONCOS-102 + novel combos**

Several opportunities: *vaccine, bi-specifics, T-cell engagers, etc…*

agenus collaboration:

Balstilimab:	anti-PD-1
Botensilimab:	Fc-enhanced anti-CTLA-4

- *Identify best combinations to further boost response rates beyond 35% ORR*
- *Simon´s two stage design*
- *Maximize opportunities for future partnering*

The cohorts can independently form the basis for subsequent registrational trial(s)

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Circular RNA pipeline program

RNA-BASED THERAPEUTICS 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

EMERGING CIRCULAR RNA TECHNOLOGY OPENS NOVEL OPPORTUNITIES FOR THE ONCOS PLATFORM

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 Bramsen,Sune B Villadsen,Aaron L Statham,Susan J C
Jørgen Kjems

circRNA discoverers are in the Targovax team

Dr. Thomas B. Hansen

Dr. Erik D. Wiklund

nature

Explore content | About the journa

nature > letters > article

Published: 27 February 2013

Natural RNA circles function as efficient microRNA sponges

Thomas B. Hansen, Trine I. Jensen, Bettina H. Clausen, Jesper B. Bramsen, Bente Finsen, Christian K. Damgaard & Jørgen Kjems

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

95k Accesses | 3825 Citations | 115 Altmetric | Metrics

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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RESEARCH CRO MEDTECH TRENDING TOPIC

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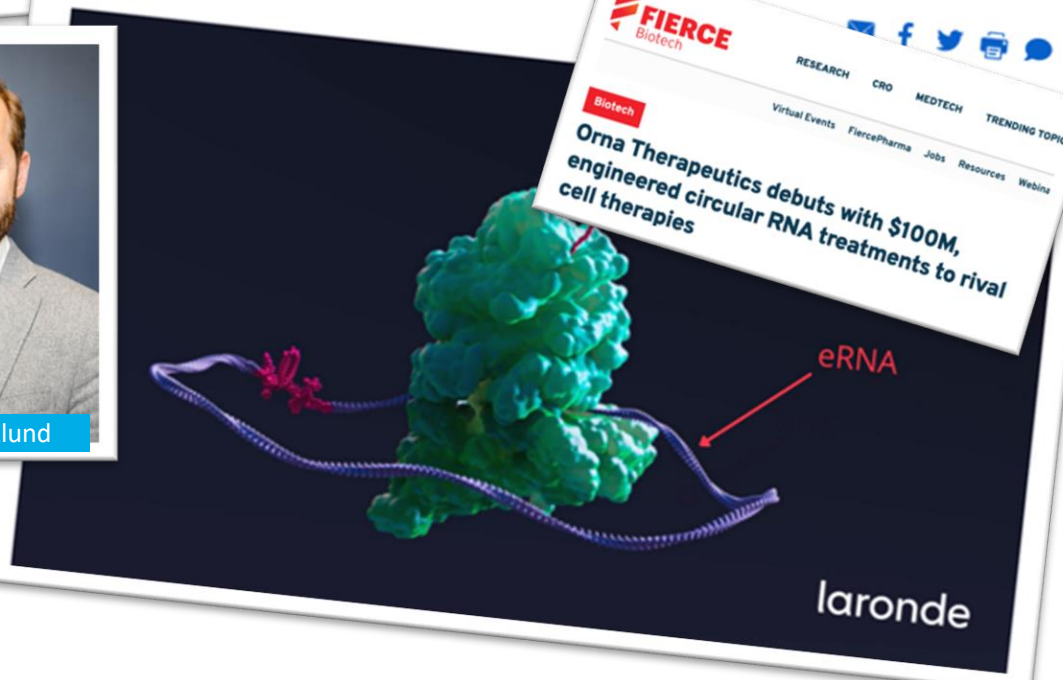
Orna Therapeutics debuts with $100M, engineered circular RNA treatments to rival cell therapies



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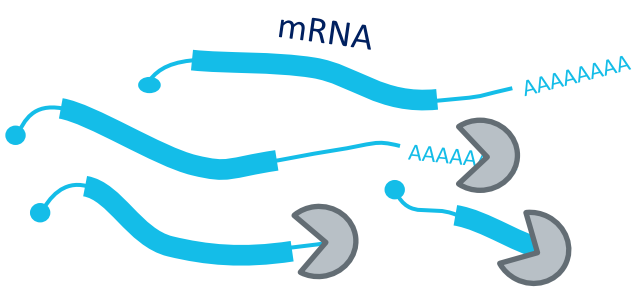
Flagship Pioneering

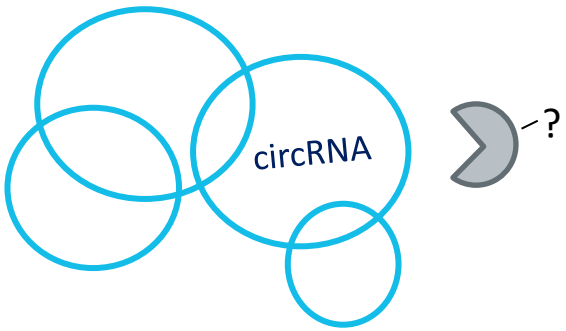
CIRCULAR RNA HAVE MULTIPLE ADVANTAGEOUS CHARACTERISTICS AS ANTI-CANCER THERAPEUTICS

Reducing *oncogenic microRNAs*

Production of proteins of choice

Circular RNA is resistant to exonuclease degradation





Transcriptional regulation *of target genes to promote cancer cell death*

Immunological activation *through pattern recognition receptors (TLR)*

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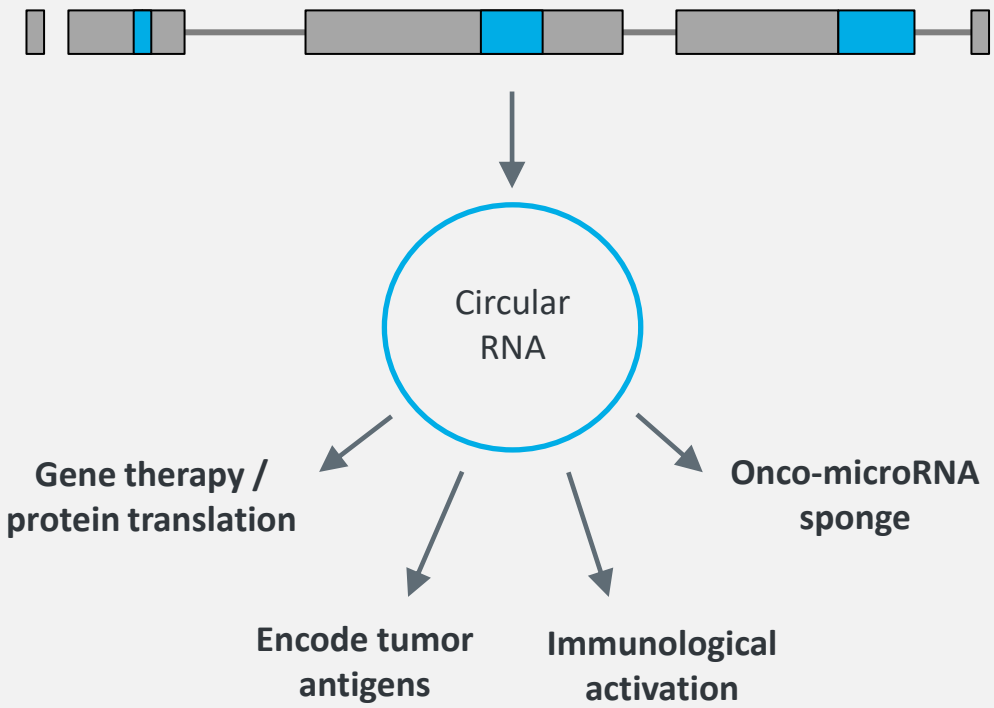
ONCOS PROVIDES A VERSATILE, CLINICALLY VALIDATED, VECTOR SYSTEM FOR CIRCULAR RNA DELIVERY

Novel ONCOS circRNA vectors



Highly verstaile delivery system

Near term objectives for circRNA program:

- **Validate advantages of circRNA**
- **In vitro proof-of-concept** data by 2H 2022
- **Solidify IP portfolio**
- Generate and assess novel **circONCOS product candidates**
- **Establish external collaborations**

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TARGOVAX´ ADVANTAGE IN HOT CIRCULAR RNA SPACE

- **Delivery system:** The ONCOS platform provides a clinically validated delivery platform for circRNA
- **Mechanistic insights:** Targovax has deep understanding of ONCOS activity based on clinical patient tumor data
- **Manufacturing:** AdV manufacturing capabilities are already in place at scale, which is not the case for circRNA
- **Team:** Targovax has recruited key expertise led by circRNA discoverer and pionéer Dr. Thomas Hansen

3 Corporate strategy

MULTIPLE PATHS TO SIGNIFICANT VALUE CREATION

Value creation strategy

ONCOS-102

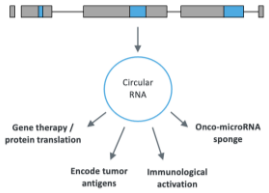
Out-license ONCOS-102 based on data from melanoma multi-cohort trial

- Opportunity to "knock-it-out-of-the-park" with novel, differentiated scientifically based IO combinations
- Sufficient sizing to de-risk program for big pharma/biotech partners
- Trial design deals with new FDA-requirements

KRAS program

Establish collaboration studies for multiple shots on goal in KRAS cancers

- Aim to initiate a portfolio of phase 1/2 trials with multiple collaboration partners in several cancer types, opening avenues for future partnering
- Combine TG vaccination with complementary immunotherapies and KRAS G12C inhibitors



Circular RNA

Pursue early pre-clinical circRNA partnering to expand into new indications

- IP portfolio strategy to enable broad circONCOS platform
- Demonstrate applicability for different types of payloads and disease settings
- Capitalize on current circRNA momentum

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1Q FINANCIAL SNAPSHOT

Key figures

Net cash flow in 1Q

- 32 / - 3.1

NOK million **USD million**

Cash at end of 1Q

150 / 15.6

NOK million **USD million**

Market cap

300 / 30

NOK million **USD million**

Daily value traded

Average last 12 months

2.3 / 0.2

NOK million **USD million**

Shareholder base

	Estimated ownership[1]	
Shareholder	**Shares million**	**Ownership**
Avanza Bank AB (nom.)	14.7	7.8 %
HealthCap	12.4	6.6 %
FJARDE AP-FONDEN	8.7	4.6 %
ABN Amro Global (nom.)	6.5	3.4 %
Nordnet Bank AB	5.3	2.8 %
Goldman Sachs & Co (nom.)	5.2	2.8 %
Nordea	4.5	2.4 %
RadForsk	4.4	2.3 %
Bækkelaget Holding	4.2	2.3 %
Danske Bank (nom.)	2.7	1.4 %
10 largest shareholders	**66.8**	**36.4 %**
Other shareholders (6 289)	119.7	63.6 %
Total shareholders	**188.3**	**100.0 %**

1 As per 29 April 2022

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TARGOVAX EXECUTIVE SUMMARY

Targovax - building the next generation immune activator therapies

- ONCOS-102: Oncolytic immunotherapy with demonstrated clinical efficacy and excellent safety profile in multiple solid tumors and treatment combinations
- Highly competitive response rate: 35% ORR in anti-PD1 refractory melanoma confirmed by deep mechanistic analyses of local and systemic immune activation
- KRAS immunotherapy: Clinical-stage polyvalent mutant KRAS vaccine with high-profile collaboration network and KRAS IO concepts in discovery phase
- Circular RNA: Emerging pipeline in novel RNA biology leveraging 10 years of academic research, potential game changer for cancer gene therapy
- Company Financials: OSE listed since 2016, raised >USD 100M in total, cash runway until mid-2023, USD 40m market cap

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STRONG, INTERNATIONAL SENIOR MANAGEMENT TEAM WITH A VERSATILE RANGE OF BACKGROUNDS

Dr Erik D Wiklund

Chief Executive Officer

Former consultant in the Pharma & Healthcare practice of McKinsey & Co and various commercial and R&D roles in biotech, Previously CFO and CBO of Targovax.

PhD Cancer epigenetics and non-coding RNA

Dr Lubor Gaal

Chief Financial Officer

BD and finance industry executive with 25 years experience from big pharma and biotech in Europe and the USA, incl. BMS, Bayer, Almirall and Locust Walk

PhD Molecular and cell biology

Dr Lone Ottesen

Chief Medical Officer

Extensive experience across the global oncology and immune-oncology drug development spectrum with nearly 20 years from AZ, GSK and others

MD, PhD

Dr Victor Levitsky

Chief Scientific Officer

Deeply experienced tumor immunology scientist from international academic and industry roles, including John´s Hopkins, Roche and Molecular Partners

PhD Virology and tumor biology

Ola Melin

Head of Manufacturing

25 years experience in Biologics development, manufacturing, and supply, most recently as Director of Technical Operations at OxThera AB.

BS Biochemical engineering

Dr Ingunn M Lindvig

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20 years in the pharma and biotech industry with extensive experience in regulatory strategy across a range of pharmaceutical products.

PhD Physiology

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