ACTIVATING THE PATIENT'S IMMUNE SYSTEM TO FIGHT CANCER

H.C. Wainwright Healthcare Conference 2022

Dr. Erik Digman Wiklund, CEO

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OSE: TRVX

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Introduction

2. Lead clinical program: ONCOS-102
3. Pipeline platform: Circular RNA
4. Outlook & strategy

THE IMMUNO-ONCOLOGY REVOLUTION

> 500,000 patients treated per year

> 3,000 ongoing clinical trials

> 40% of US cancer patients eligible

> 10 approved products

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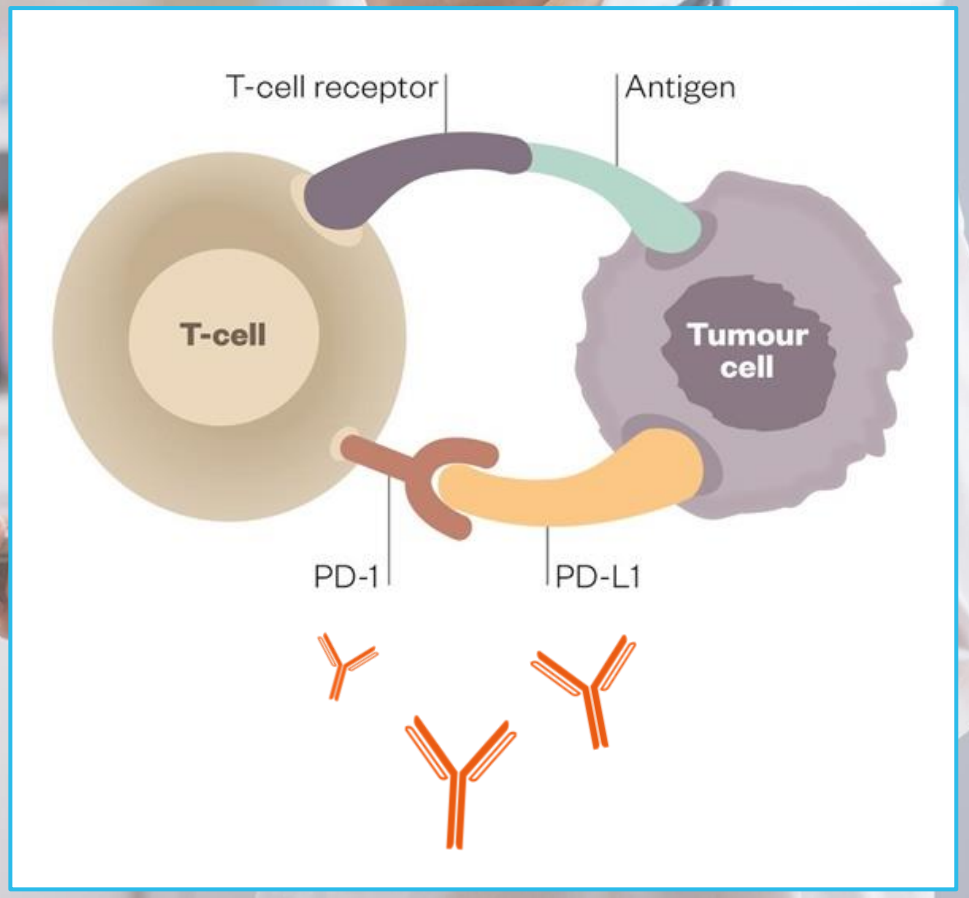
FIRST GENERATION IMMUNO-ONCOLOGY: CHECKPOINT INHIBITORS

Cornerstone of current cancer treatment

Deep and durable responses

$30b annual sales globally

8 products approved to date, many more in development



SOURCE: GlobalData, Research&Markets

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THE CHALLENGE:

MAKE PD-1 CHECKPOINT INHIBITORS WORK FOR MORE PATIENTS

0-40% of treated patients respond

>50% of responding patients relapse

1 PD-1 checkpoint inhibitor monotherapy not sufficient

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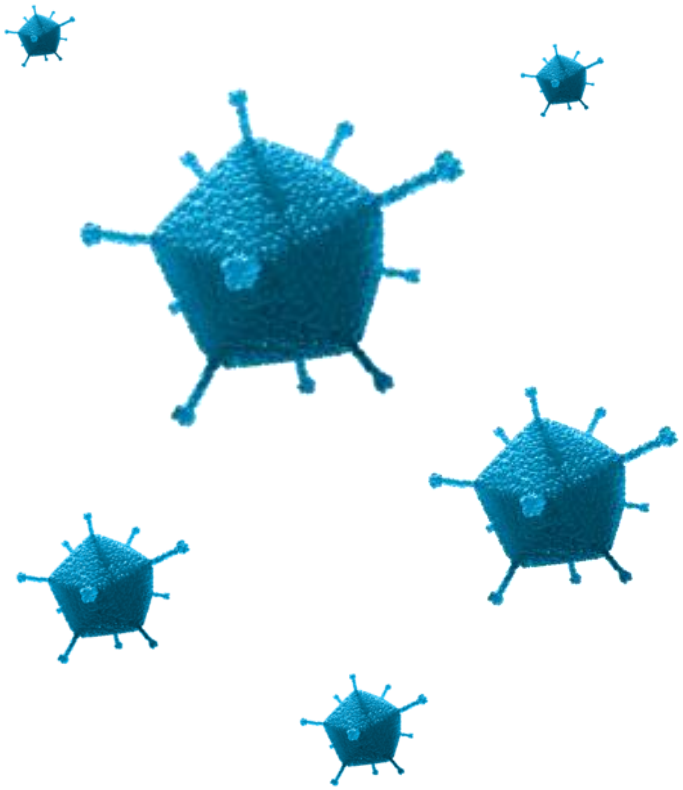
THE SOLUTION: IMMUNE ACTIVATION BY TARGOVAX´S ONCOLYTIC VIROTHERAPY ONCOS

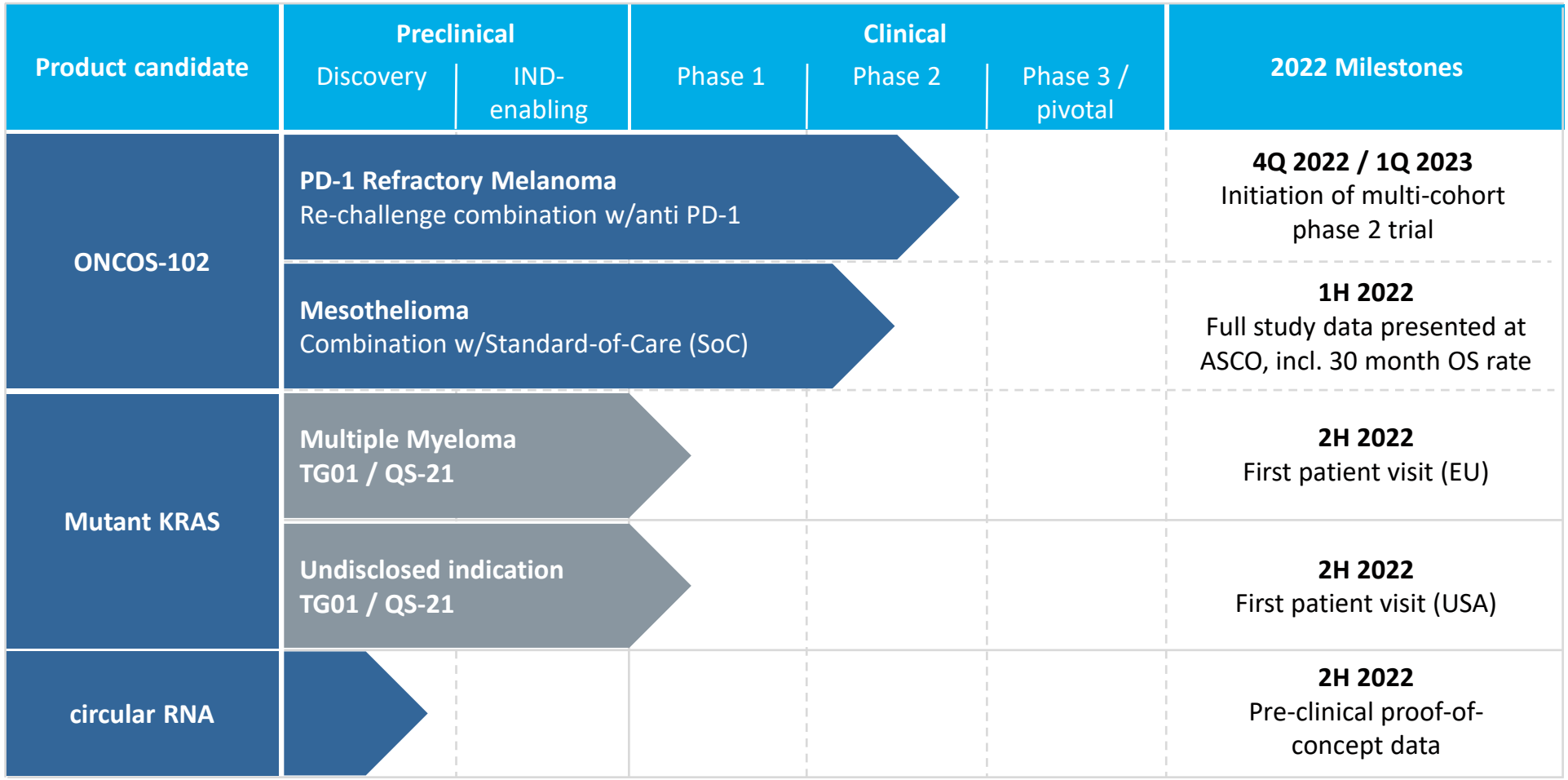


Reverses immuno-suppressive defence mechanisms in the tumor

Primes anti-cancer T-cell responses

Delivers immune stimulatory payloads

TARGOVAX DEVELOPMENT PIPELINE



Trials run and financed by collaboration partners

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Lead clinical program: ONCOS-102

TARGOVAX DEVELOPMENT PIPELINE

Product candidate	Preclinical		Clinical			2022 Milestones
	Discovery	IND-enabling	Phase 1	Phase 2	Phase 3 / pivotal	
ONCOS-102	**PD-1 Refractory Melanoma** Re-challenge combination w/anti PD-1					**4Q 2022 / 1Q 2023** Initiation of multi-cohort phase 2 trial
	Mesothelioma Combination w/Standard-of-Care (SoC)					**1H 2022** Full study data presented at ASCO, incl. 30 month OS rate
Mutant KRAS	**Multiple Myeloma** **TG01 / QS-21**					**2H 2022** First patient visit (EU)
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circular RNA						**2H 2022** Pre-clinical proof-of-concept data

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PD-1 RESISTANCE MARKET OPPORTUNITY

GROWING UNMET NEED WITH INCREASED ANTI-PD-1 USE

Incidence	Total **~50,000 patients per year** diagnosed with unresectable advanced malignant melanoma globally
PD-1 resistance	~50% of cases become PD-1 resistant Total **~25,000 patients per year**
Addressable	**Estimated 10,000 – 20,000 patients per year** addressable with intra-tumoral therapies
Other PD-1 resistance	***>100,000 patients per year lung cancer*** ***>50,000 patients per year head and neck***

SOURCE: GlobalData, Targovax analysis

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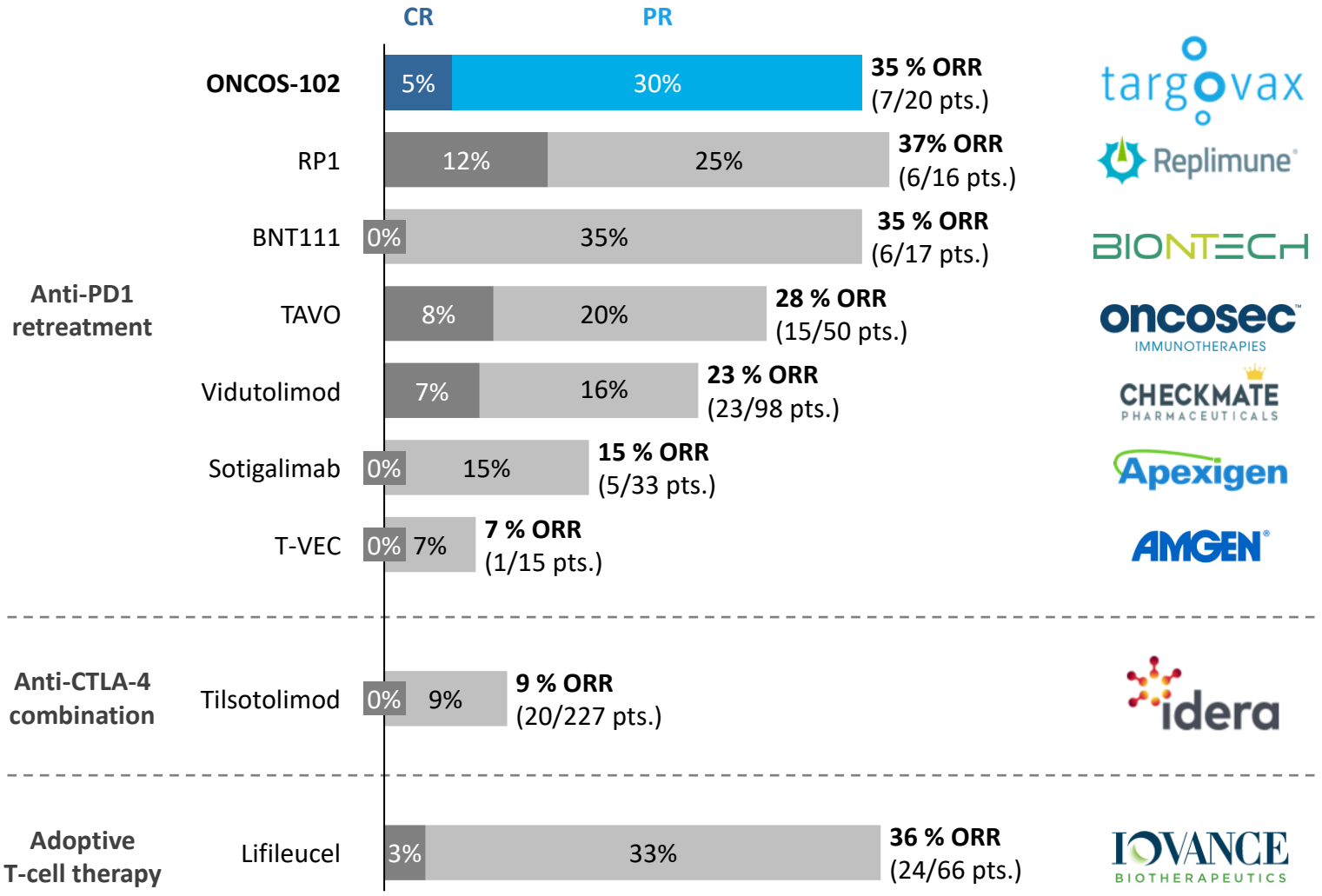
ONCOS-102 ACHIEVED A HIGHLY COMPETITIVE ORR OF 35% IN A PD-1 REFRACTORY MELANOMA PHASE 1

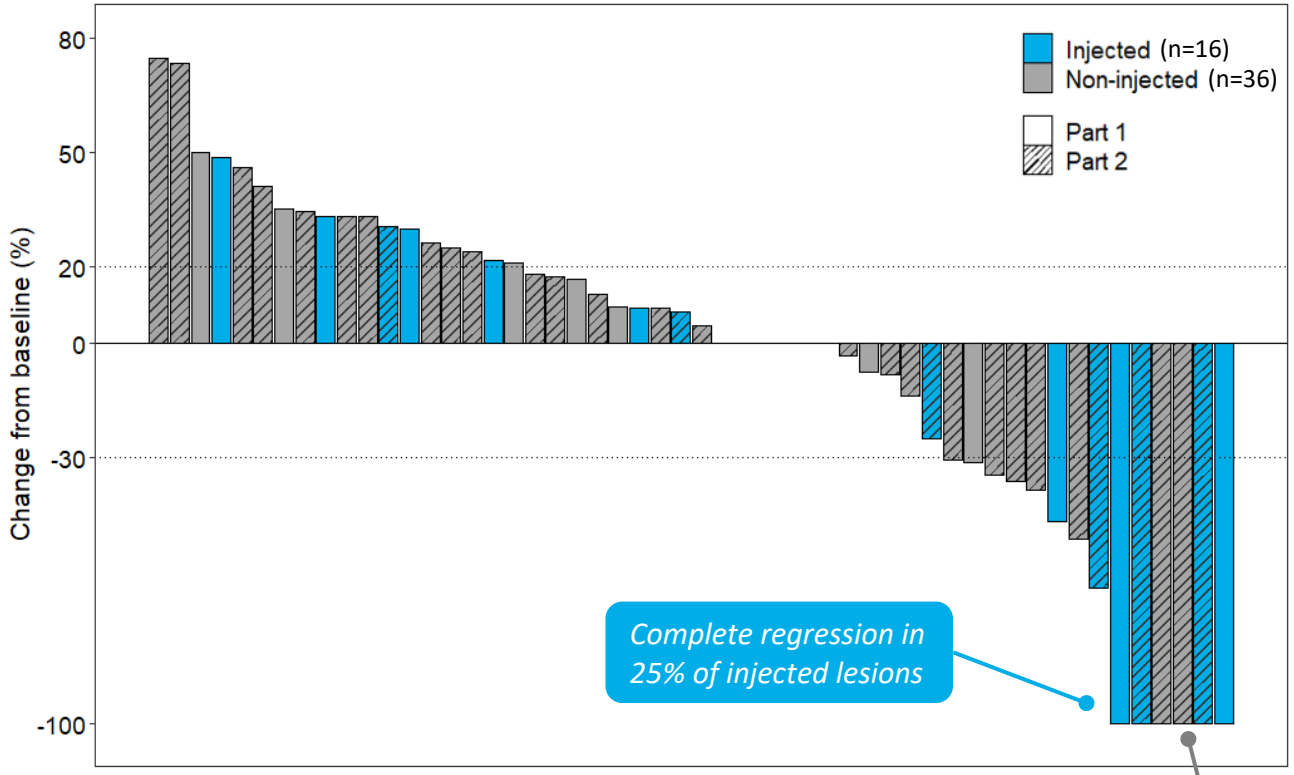


Targovax market analysis, June 2022

LOCALLY DELIVERED ONCOS-102 GENERATES ROBUST SYSTEMIC ACTIVITY

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
- **6 of 15 patients (40%)** with abscopal objective response (PR) according to RECIST 1.1 30% tumor shrinkage criteria

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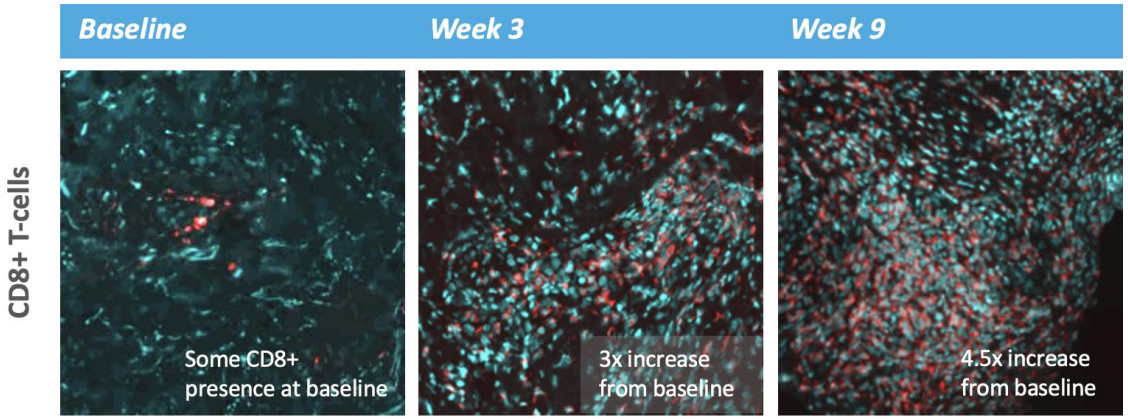
ONCOS-102 DRIVES STRONG AND CONSISTENT T-CELL INFILTRATION IN RESPONDING PATIENTS

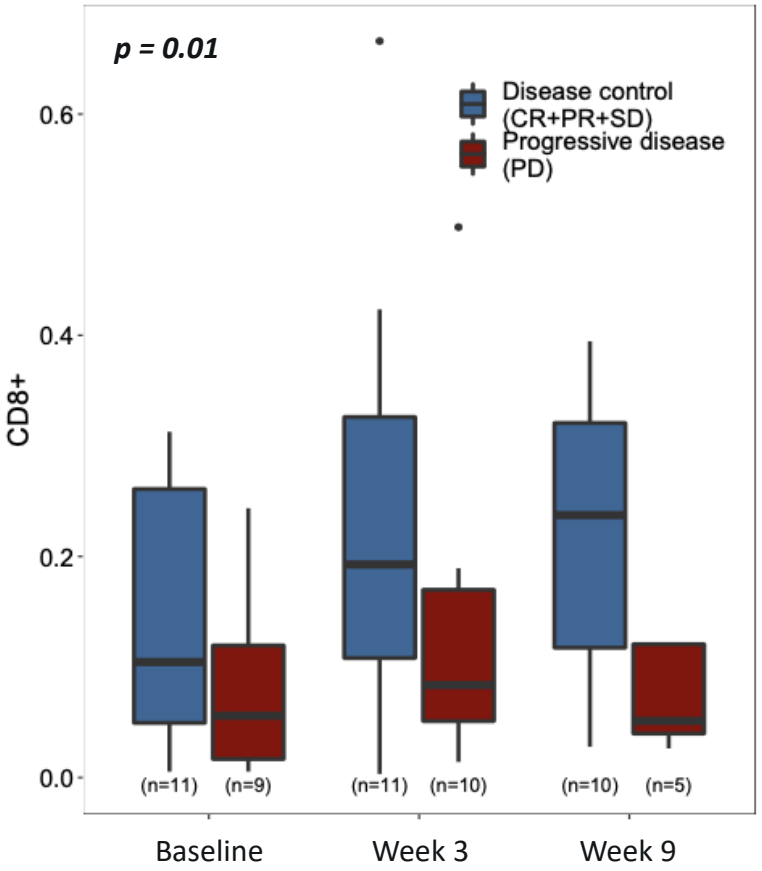
CD8+ T-cell tumor infiltration
Tumor biopsy IHC, patient case example



Progression on pembrolizumab	3x ONCOS-102 only monotherapy	6x ONCOS-102 2x pembrolizumab

Prior therapies:	T-vec (oncolytic virus) Ipilimumab (aCTLA-4) Pembrolizumab (aPD-1)	**Disease stage:**	T4a-M1
		Outcome:	PR RECIST 1.1 Week 9 - EoS

CD8+ T-cell infiltration increased over time in patients with clinical benefit (CR+PR+SD)



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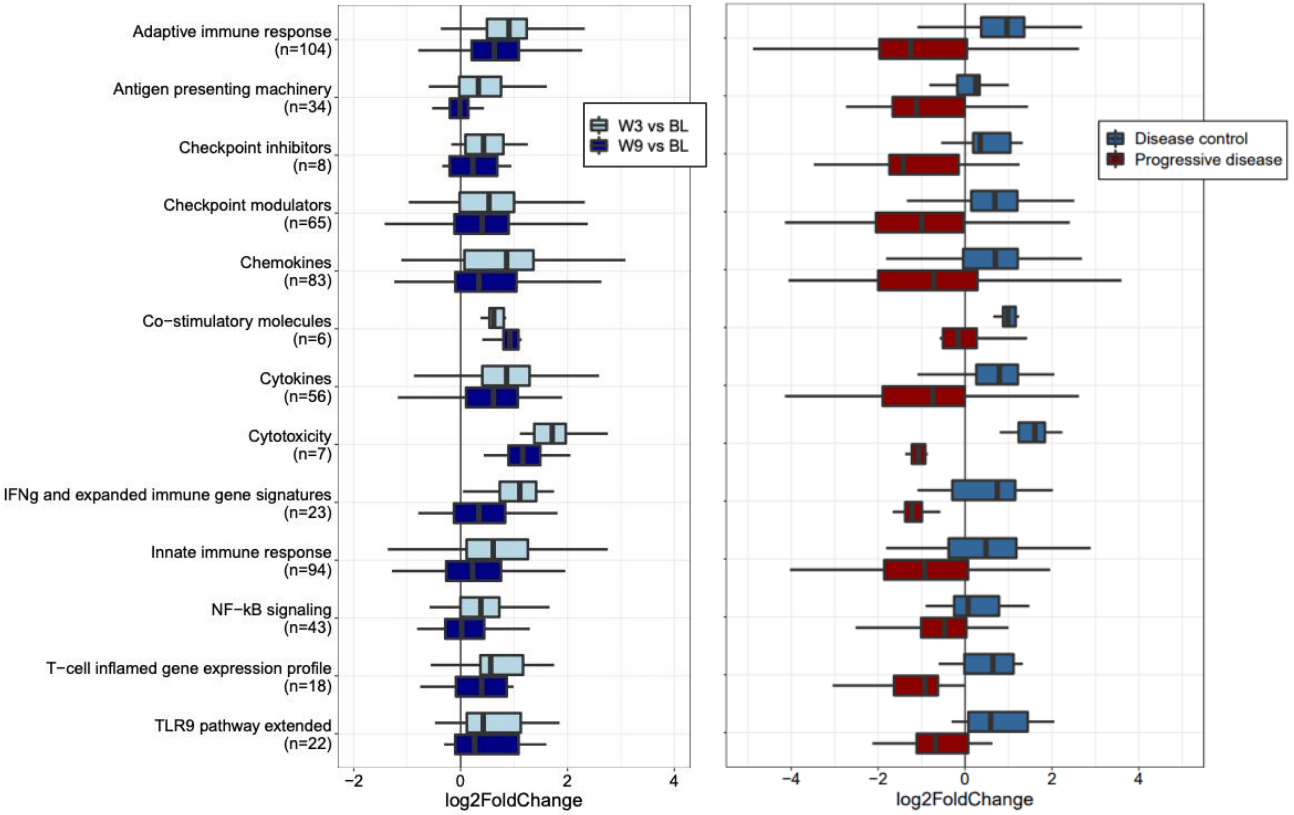
GENE EXPRESSION CONFIRMS CELLULAR ANALYSES, REVEALING BROAD PRO-INFLAMMATORY TUMOR RE-PROGRAMING

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 long-term** over multiple local 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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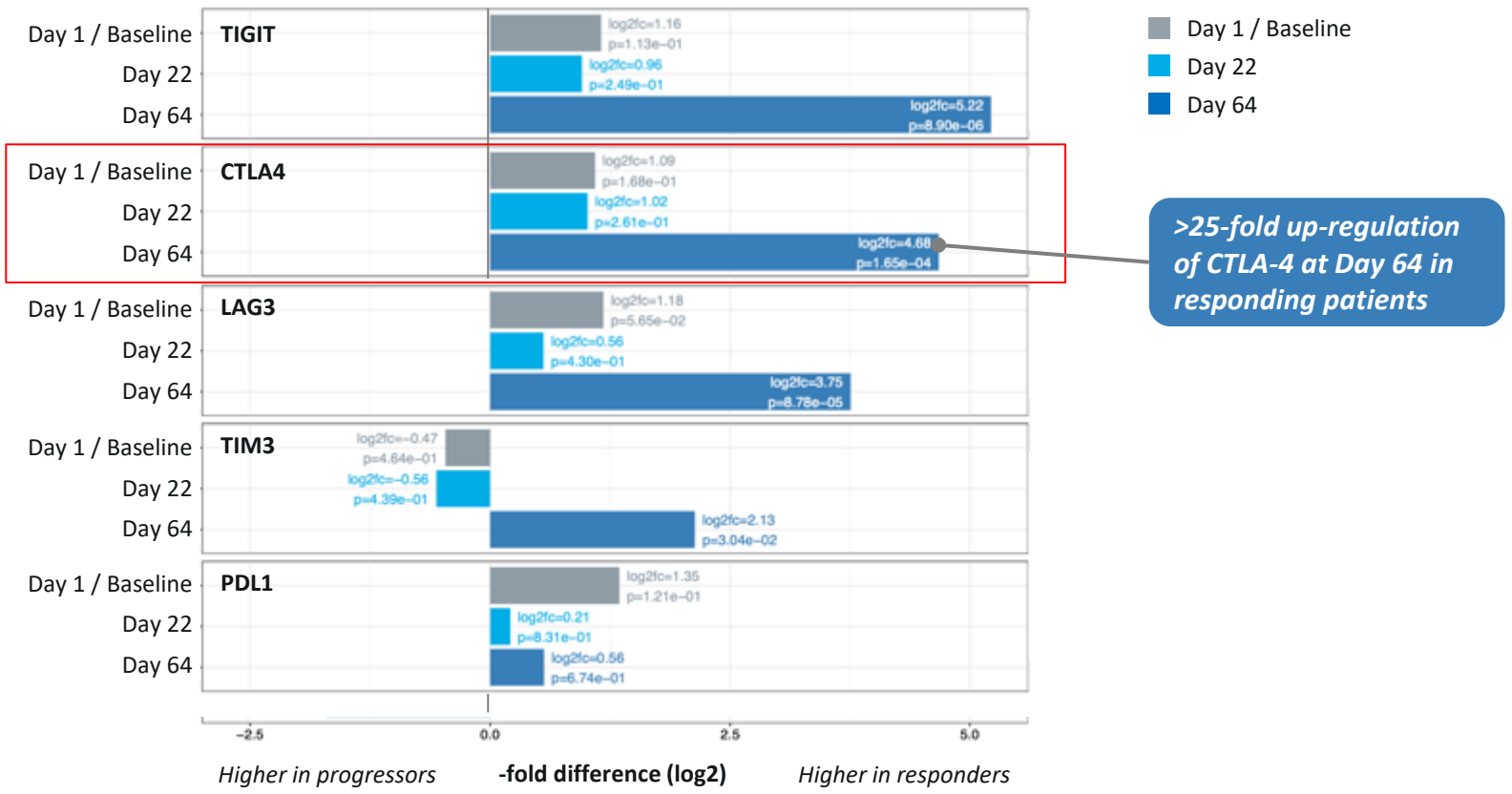
CTLA-4 IS STRONGLY UPREGULATED IN RESPONSE TO ONCOS-102 IN MELANOMA

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



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STRONG RATIONALE FOR COMBINING ONCOS-102 ALSO 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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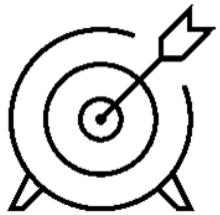

Enhance anti-tumor T-cell priming

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

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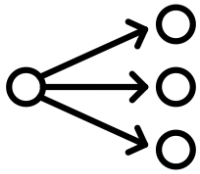

Boost systemic activity

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

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NEXT STEP ONCOS-102: MULTI-COHORT PHASE 2 TRIAL WITH 2ND GEN CTLA-4 CHECKPOINT INHIBITOR COMBINATION

Part 1 – higher dose exploration run-in

1 **ONCOS-102** monotherapy high dose[1]

Randomize

2 **ONCOS-102 + balstilimab** low[2] → high dose

- *Confirm safety*
- *Select dose for expansion*

→

- *10 patients per cohort to start*
- *Extend selected dose to n=18*

Part 2 – multi-cohort extension

2 **ONCOS-102 + balstilimab** high dose[3]
- *Expand to n=37*

3 **ONCOS-102 + botensilimab**
- *Safety run-in n=6*
- *Expand first to n=18, then n=37*

4 **ONCOS-102 + balstilimab + botensilimab**
- *Safety run-in n=6*
- *Expand first to n=18, then n=37*

Collaboration partner: agenus

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

1: High dose: $1x10^{12}$ viral particles (VP)
2: Low dose $3x10^{11}$ VP
3: High dose expected selection for Part 2

BOTENSILIMAB IS A NOVEL CTLA-4 CHECKPOINT INHIBITOR OFFERING SEVERAL ADVANTAGES OVER 1ST GEN aCTLA-4

Improved safety

- Designed for **reduced activation** of the **complement cascade**, lowering immune-mediated adverse events
- Emerging differentiated safety profile vs. ipilimumab with **low rates of tox discontinuation** (mono & combo)

Stronger immune activation

- **Improved stimulation of antigen presenting cells** (APCs and DCs) boosts immune activation
- **Engineered for enhanced binding** to broader set of activating **Fcγ-receptor variants** than ipilimumab

Better efficacy

- **Strong responses observed** in several tumor types
- Monotherapy **responses shown** in prior PD-1 +/- CTLA-4 (incl. ipi/nivo) failures in **melanoma**
- **Unprecedented 24% ORR in MS-stable metastatic colorectal cancer** in combination with anti-PD1

SOURCE: Agenus

THE PHASE 2 TRIAL IS DESIGNED TO ENABLE FUTURE OUT-LICENSING AND ADDRESS REGULATORY REQUIREMENTS

- ✓ Opportunity to achieve **best-in-class data**
- ✓ **Differentiated combinations** vs. competitors, with strong scientific and strategic rationale
- ✓ **Design and size** to **enable licensing decisions** for big pharma partners
- ✓ **Confirm ONCOS-102 high dose** and address FDA requirements for contribution of components
- ✓ Support future **expansion of combinations into earlier lines** of melanoma

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Pipeline platform: Circular RNA

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Trials run and financed by collaboration partners

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EMERGING CIRCULAR RNA TECHNOLOGY OPENS NOVEL OPPORTUNITIES FOR CANCER IMMUNOTHERAPY

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

Jørgen Kjems

The circRNA discoverers work for Targovax

Dr. Thomas B. Hansen

Dr. Erik D. Wiklund

nature

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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.

BIOTECH

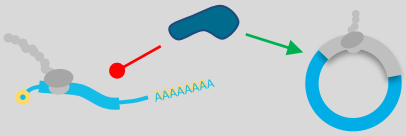
Merck bets big on circular RNA, paying $150M to work with Orna

Orna revealed a double dose of good news, taking the lid off an alliance with Merck worth $150 million upfront and a $221 million series B round.

moderna

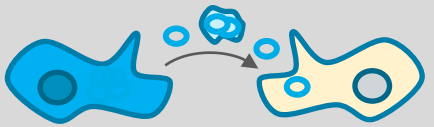
Flagship Pioneering

circRNA PROVIDES A TOOLBOX TO TAKE CANCER IMMUNOTHERAPY TO THE NEXT LEVEL

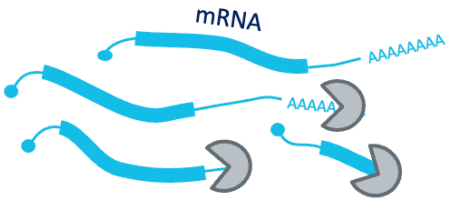


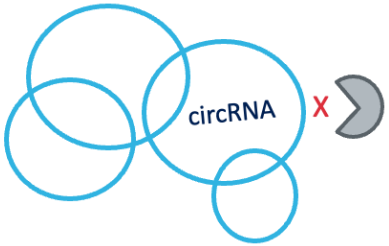
Maximize payload expression

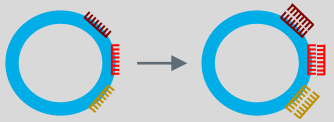
Extra-cellular trafficking



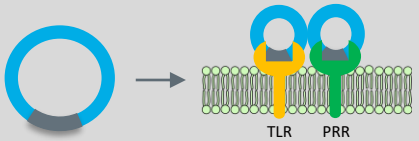
Circular RNA is resistant to exonuclease degradation, leading to vastly increased half-life







Onco-microRNA sponging



Immune response booster

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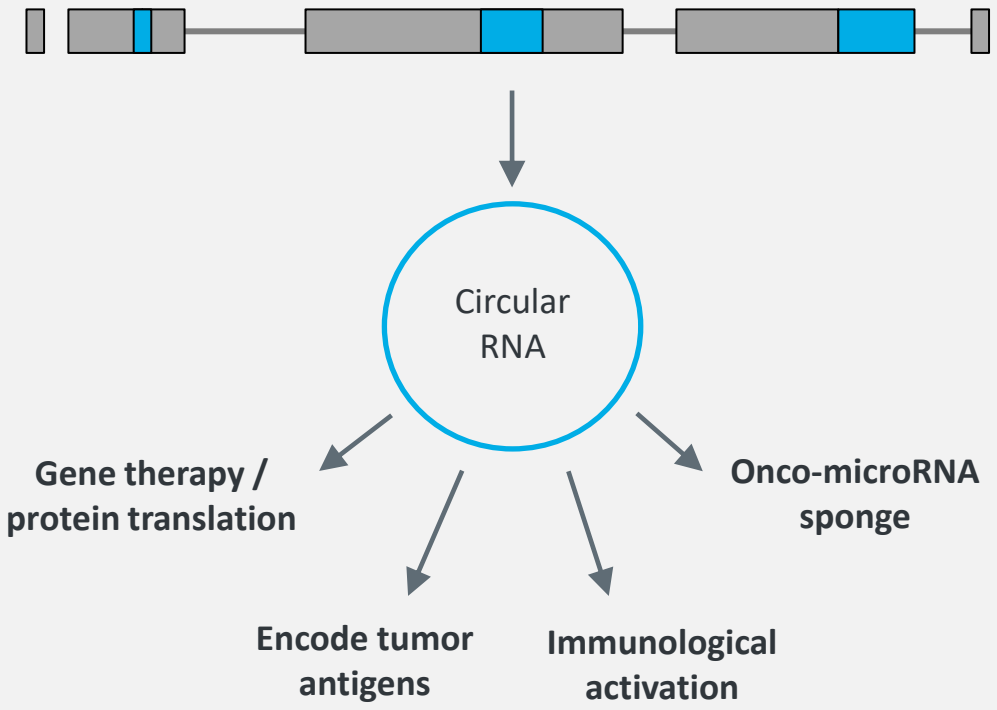
TARGOVAX HAS A CLINICALLY VALIDATED, VERSATILE VECTOR SYSTEM THAT WILL BE DEPLOYED FOR CIRCRNA DELIVERY

Targovax circRNA vectors



Objectives for circRNA program:

- Validate advantages of circRNA approach
- Optimize expression constructs
- Select and optimize payloads
- Generate proof-of-concept data
- Build strong IP portfolio
- Establish external collaborations

Highly verstaile delivery system – Broad functionality

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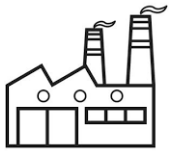
TARGOVAX HAS A UNIQUE EDGE IN THE EMERGING circRNA SPACE

World-leading circRNA experts in-house with deep technical experience

- Head of program is circRNA discoverer Dr. Thomas Hansen, the pionéer of early circRNA research with over 10 years experience in the field

Clinically validated vector system for intra-tumoral RNA delivery

- Synthetic circRNA faces the same delivery issues as mRNA, relying on LNP systems with limited ability for tumor targeting



GMP vector manufacturing process scale-up already ongoing

- Validated technology for synthetic circRNA GMP manufacturing at scale does not yet exist and faces unresolved challenges

No known competitors active in circRNA therapeutics for solid tumors

- Building on deep translational data from prior ONCOS-102 trials

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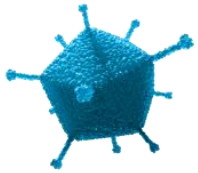
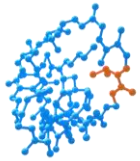
Outlook & Strategy

OUTLOOK: MULTIPLE PATHS TO VALUE CREATION

Pillar	Value creation strategy
 **ONCOS-102**	**Out-license ONCOS-102 with results from phase 2 melanoma trial** ○ Aim to “knock-it-out-of-the-park” with novel triple combination ○ Study designed and sized to be attractive for big pharma partners
 **KRAS program**	**Create broad optionality and multiple shots on goal in KRAS cancers** ○ Two academically sponsored TG01 trials set to open during 2H 2022 ○ Collaborative networks being established in several cancers and combinations
 **Circular RNA**	**Pursue early pre-clinical circRNA partnering** ○ Capitalize on current circRNA momentum ○ Strategy to enable broad circRNA platform and future pipeline engine

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