ONCOLYTIC VIRUSES OVERVIEW

Targovax Presentation at

World Vaccine Congress

Europe 2022

14 October 2022

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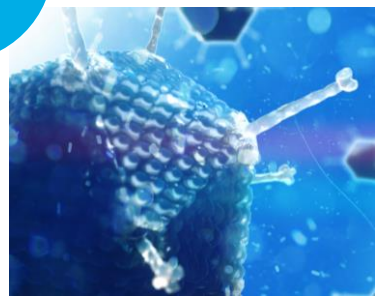
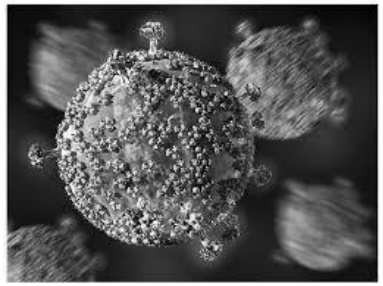
TARGOVAX AIMS TO ACTIVATE THE PATIENT'S OWN IMMUNE SYSTEM TO FIGHT CANCER

Targovax focus





Immune activators

Oncolytic viruses, vaccines

Immune modulators

Checkpoint inhibitors

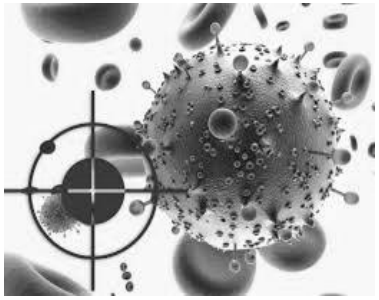
Surgery - Radio - Chemo

Cell therapy

CAR-Ts, TCRs

Targeted therapy

TKIs, PARPs, etc.



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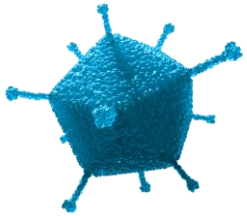
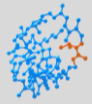
TARGOVAX HAS TWO CLINICAL STAGE IMMUNE ACTIVATOR PROGRAMS



ONCOS
Oncolytic virus

- Genetically **armed adenovirus**
- **Clinically demonstrated powerful** innate and adaptive **immune activation**
- **Efficacy in combination with both anti-PD1 and chemotherapy**



TG
Neoantigen vaccine

- **Shared mutant RAS neoantigen** therapeutic cancer vaccine
- Triggers **T-cell responses** to oncogenic **RAS driver mutations**
- 32 patient **phase I/II trial completed**
- Next generation TG program contingent upon **funding from Innovation Norway**

Activates the immune system

Triggers patient-specific responses

No need for personalization

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Oncolytic Virus Landscape Overview

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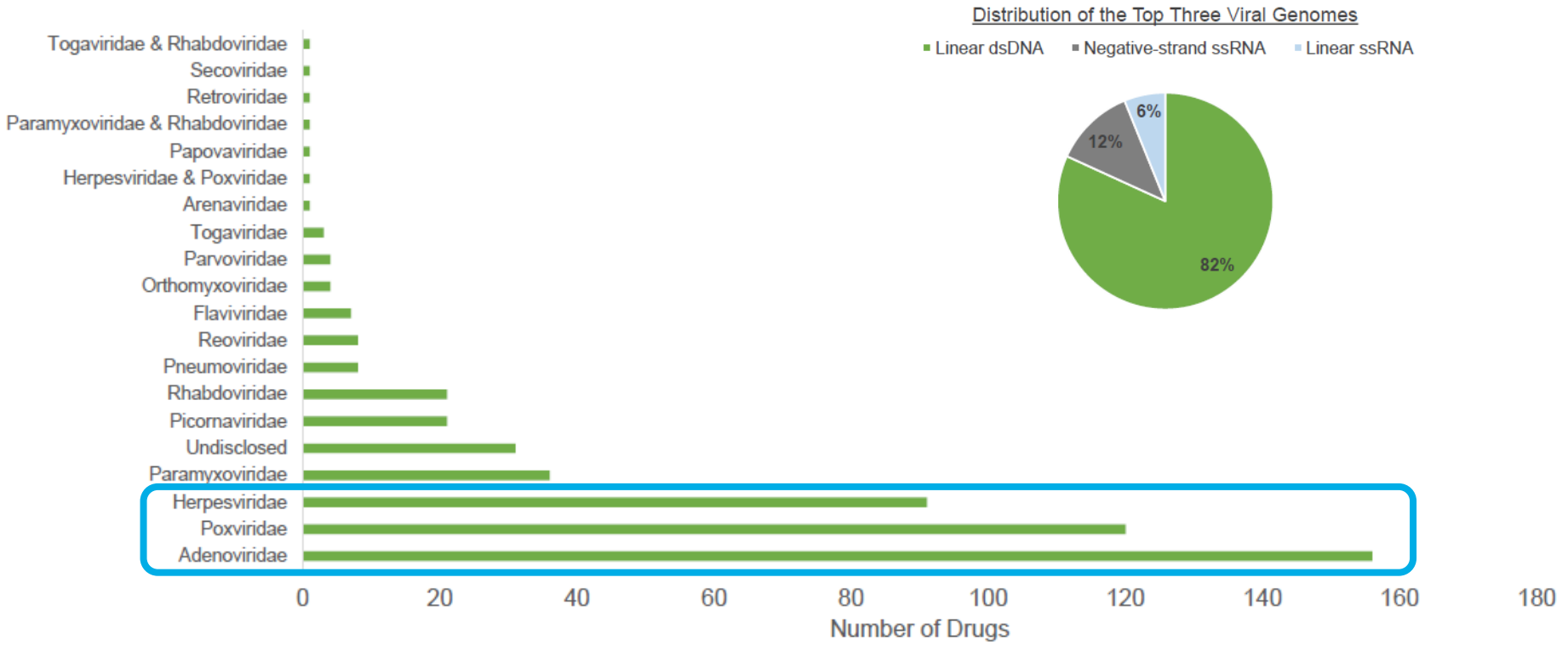
~550 PROGRAMS - MANY VIRAL FAMILIES

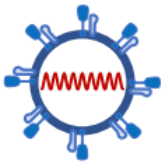
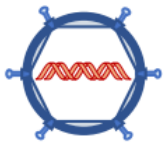
- No such thing as one OV, many subtypes with big differences
- Adenovirus are the largest OV family, followed by vaccinia and herpes simplex virus
- These are double-stranded DNA viruses, representing the majority of all OVs



www.beacon-intelligence.com

SOURCE: Beacon Intelligence, report “Oncolytic virus H1 landscape 2022”

MOST COMMON OV CHARACTERISTICS

	Herpesvirus	Adenovirus	Vaccinia Virus	Measles Virus	Reovirus
Structure					
Genome	152kb dsDNA	36kb dsDNA	190kb dsDNA	16kb ss(-)RNA	23kb dsRNA
Virion Size	200 nm	70-90 nm	70-100 nm	100-200 nm	75 nm
Receptor	HVEM, nectin1/2, HSPG	CAR, CD46, DSG-2	glycosaminoglycans/ laminin, MARCO	CD46	carbohydrates, JAM-A

Size

Immunogenicity

Virus type	Description	Pros	Cons
Herpes virus	Large envelope DNA virus, large payload, long DNA sequences,	Only approved OV virus class, **highest DNA payload capacity**, easily manipulated	**Weak innate immune response**, long latency, long/permanent infectivity
Vaccinia virus	Large envelope DNA virus, large payload, long DNA sequences,	Well-known vector, can **carry large transgenes** (25 kb), extra-nuclear replication	Large size, **slow replication, rapid neutralization**, failed in late-stage trials
Adeno-virus	Mid-size non-enveloped DNA virus, ability to carry some payload DNA sequences	Extensively studied**, well tolerated**, **immunogenic,** innate immune system	Highly immunogenic**, creates nAbs after IV admin** (in naked form), lower payload
Small RNA viruses	Small RNA genome, usually non-enveloped, limited ability to carry transgenes (except VSV)	**High oncolytic potency**, rapid replication, strong innate response	Safety issues seen with too potent lysis (VSV virus), limited platform versatility

SOURCE: Watanabe *et al* 2021, Molecular Therapy

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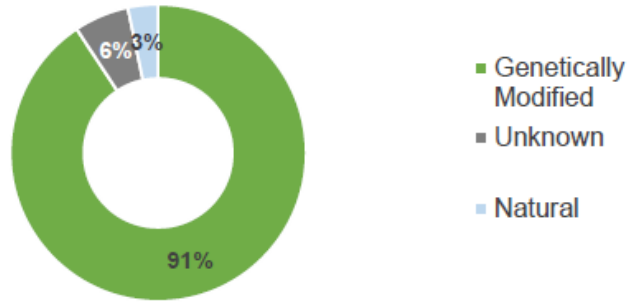
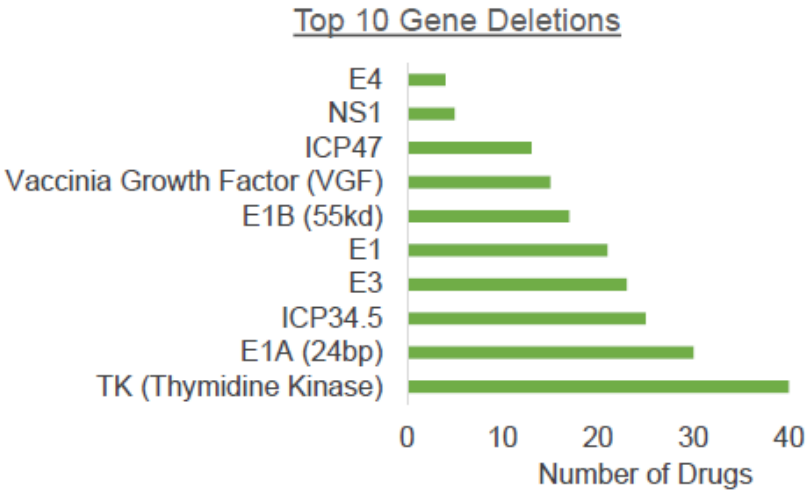
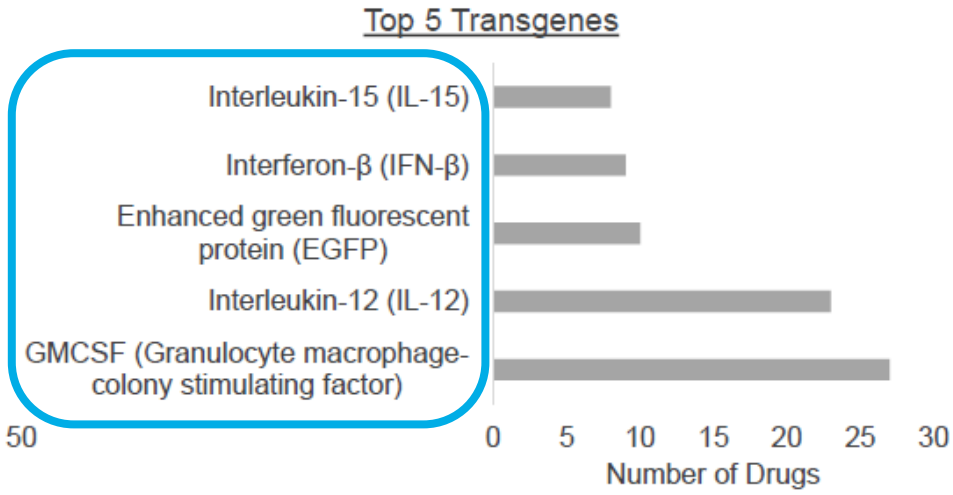
VARIOUS AVAILABLE MODIFICATIONS OF OV

- Majority of OV products are genetically modified
  - → Deletions to increase tumor cell selectivity
  - → Additions to increase immune stimulation





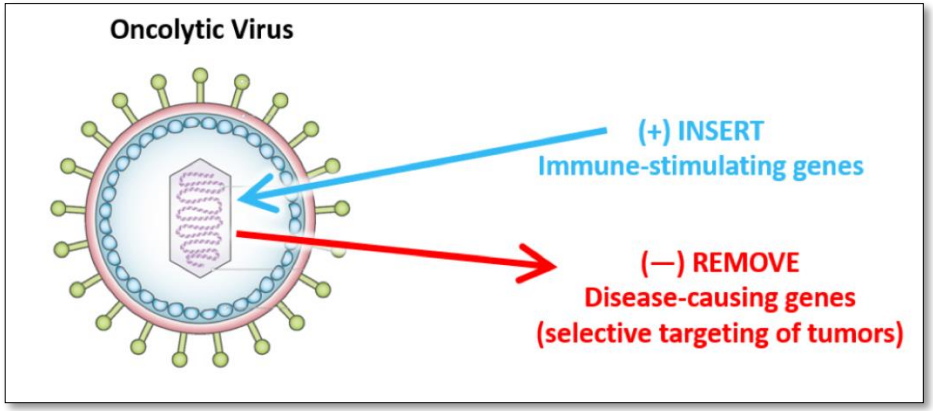


SOURCE: Beacon Intelligence, report "Oncolytic virus H1 landscape 2022"

KEY DIFFERENCES BETWEEN VARIOUS OV

Key differences between OV products

- Viral backbone (affecting entry receptors, replication and oncolytic capacity)
- Immunogenicity
- Transgene expression
- Payload



Modifications:

→ Enhancing tumour tropism (improve selective entry into tumor cells)

→ Increase safety, restricting replication to cancer cells

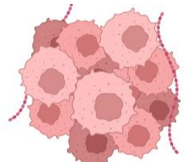
→ Increase immunogenicity (increase TLR stimulation for example)

→Transgene expression to increase efficacy (various categories)

SOURCE: Hemminiki *et al* 2020, Journal of Hematology & Oncology, cancerresearch.org (Sep 2022)

ONCOLYTIC VIRUS TRANSGENE CATEGORIES

Transgene category	Examples
○ Signalling molecules: cytokines/chemokines	GM-CSF, IL-12, CXCL10, IFNß
○ Co-stimulatory molecules	CD40L, 4-1BBL, OX40L
○ Anti-co-inhibitory molecules	Anti-CTLA-4, anti-PD-1
○ Targeting tumour microenvironment/stroma	Hyaloronidase, HPGD
○ Anti-tumour antigens	Anti-FAP, EGFR
○ Reporter transgenes (to enable tracking)	GFP
○ Increasing efficacy by other drugs	hNIS (concentrating radioiodine) FCU1 (chemotherapy)



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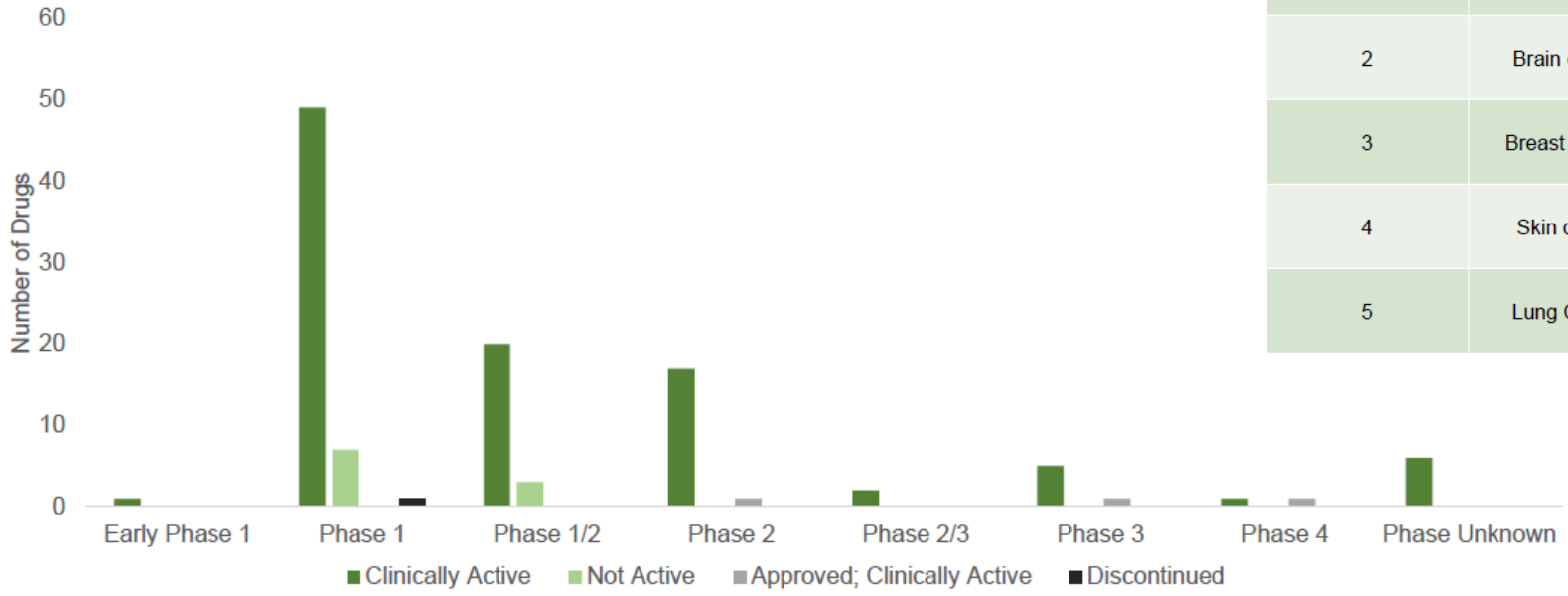
DELIVERY AND INDICATIONS

- Majority of OV products are delivered intratumorally but there are several aiming for intravenous delivery
- Majority of OV products are in early stages of development
- Majority are targeting solid tumours

Highest phase of development and status distribution of OV therapies



Rank	Preclinical	Clinically Active
1	Pancreatic Cancer	Brain cancer
2	Brain cancer	Skin cancer
3	Breast Cancer	Breast Cancer
4	Skin cancer	Lung Cancer
5	Lung Cancer	Head and Neck Cancer

SOURCE: Beacon Intelligence, report “Oncolytic virus H1 landscape 2022”

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Oncolytic virus

ONCOS 102 OVERVIEW

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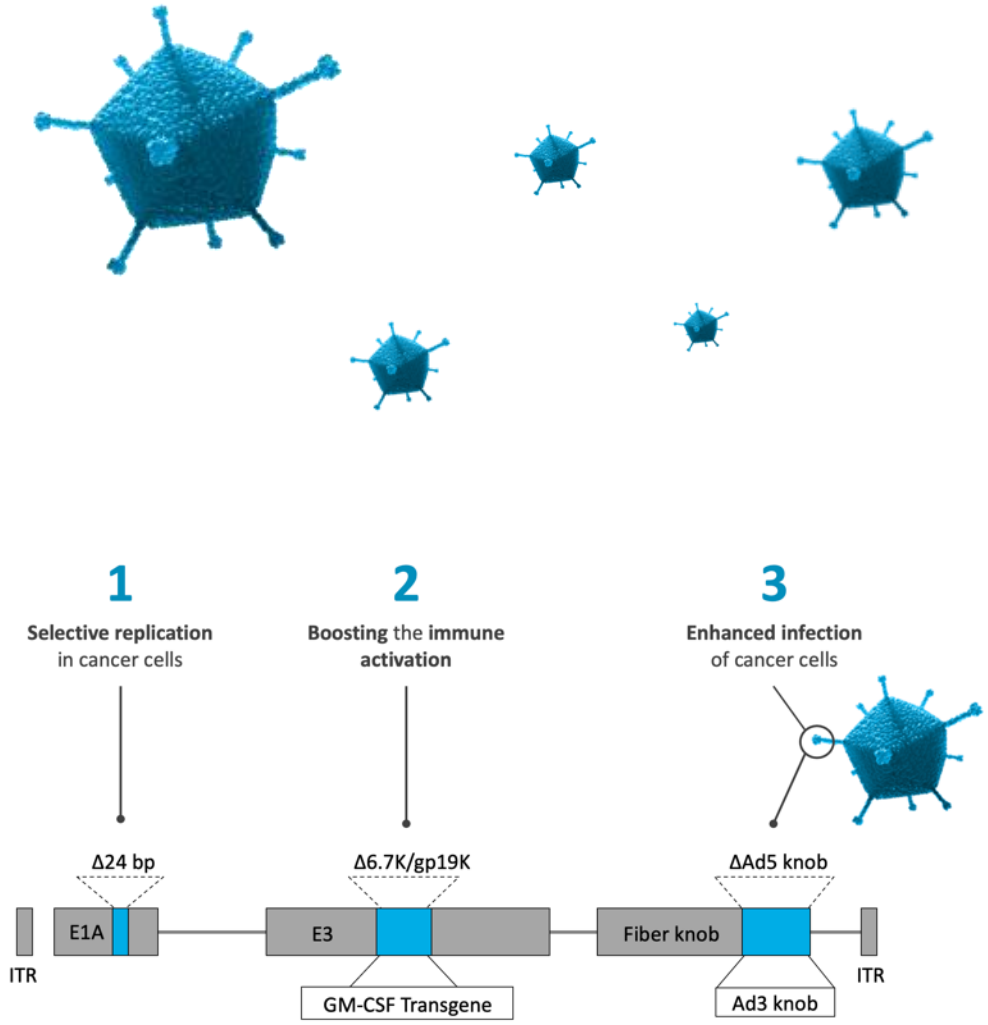
ONCOS-102 – ONCOLYTIC ADENOVIRUS

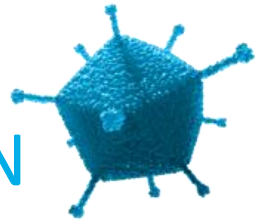


Reverses immuno-suppressive defence mechanisms in the tumor

Primes anti-cancer T-cell responses

Delivers immune stimulatory payloads

ONCOS-102 – VARIOUS MECHANISMS OF ACTION



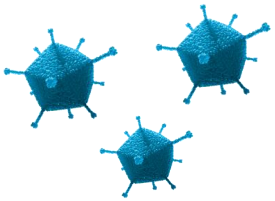
The suggested MoA include:

ONCOS-102 infection of tumor cells

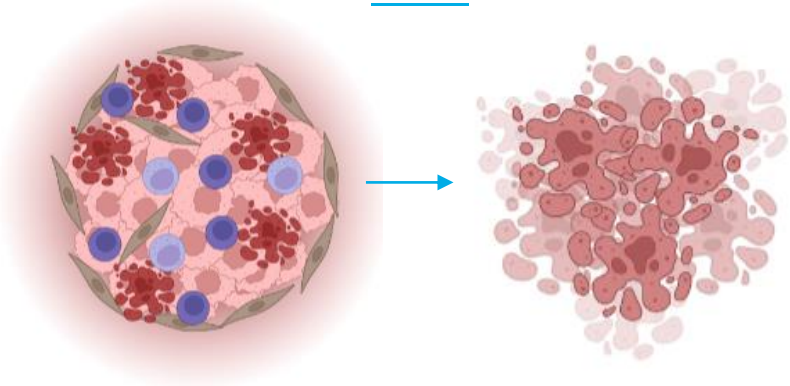
- Replication in tumor cells → Oncolysis → Immunogenic cell death: release of cancer antigens
- Virus-induced sensing pathways (PAMP/DAMP) → Innate immune stimulation (DCs, monocytes, etc) → ↑ Inflammatory signaling; ↑ Antigen presentation, co-stimulation
- Local production of GM-CSF → NK cell activation

T-cell priming, activation and ↑ infiltration

Anti-tumor effect



Goals:



Turning cold into hot

Tumor cell death

SOURCE (image): Biorender

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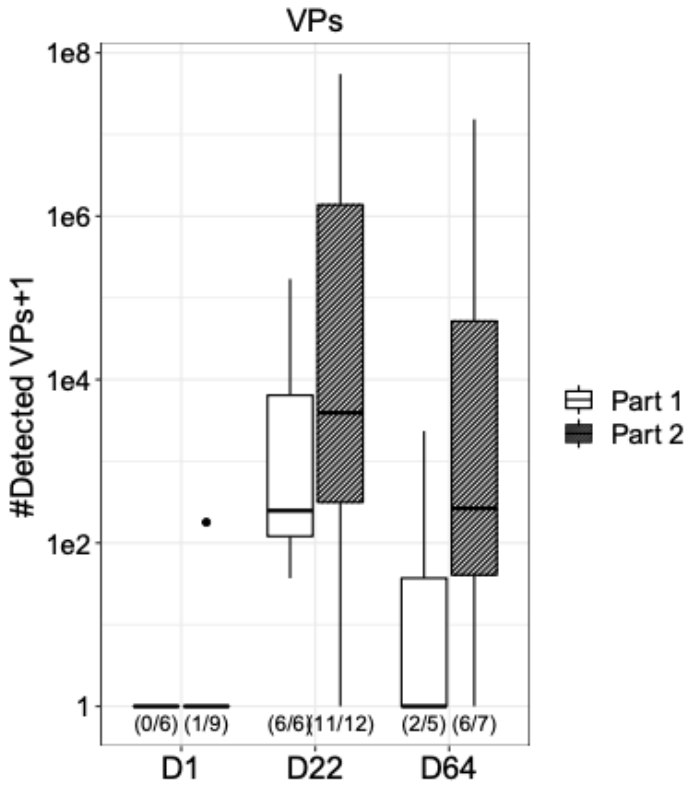
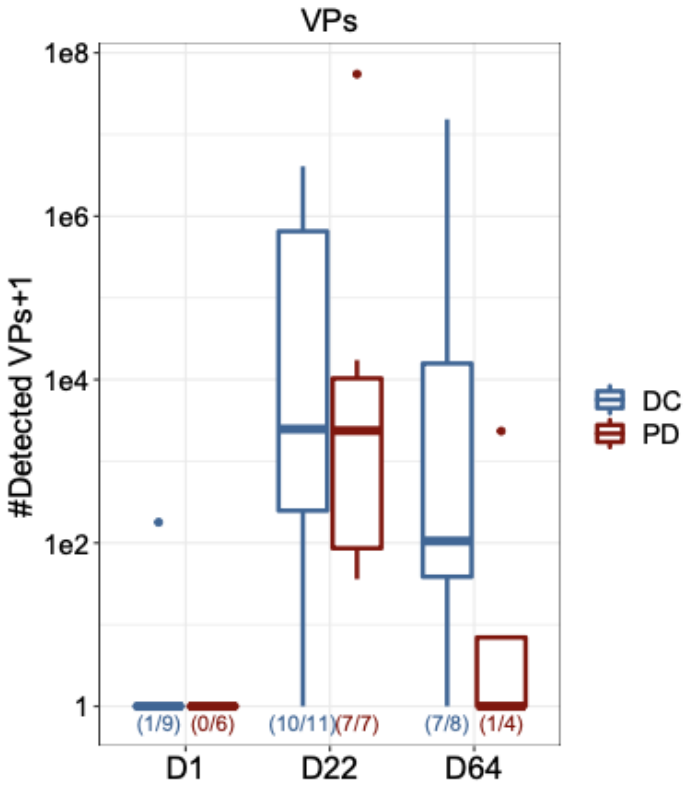
ONCOS-102 IS ROBUSTLY DETECTABLE IN TUMORS AND REMAIN PRESENT IN RESPONDERS AT LEAST UNTIL WEEK 9

ONCOS-102 viral particles (VP) in tumor, qPCR on tumor biopsy DNA

Part 1 vs. Part 2 patients



Patients w/DCR vs. PD



- **High ONCOS-102 levels** observed at week 9 in **responding tumors**
- **More virus** detected in **Part 2** patients (concomitant dosing)
- **Virus replication** in the tumor at least beyond 6 injections up **until week 9** (last data point)

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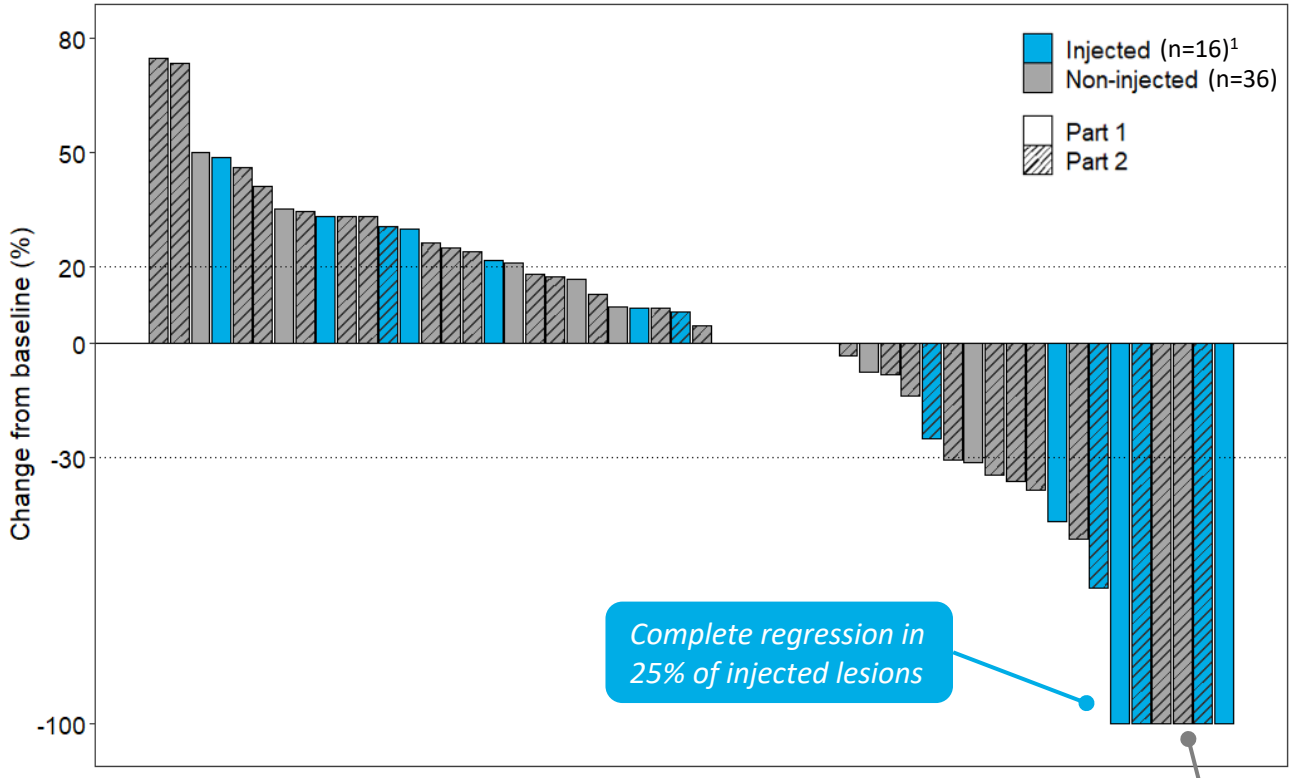
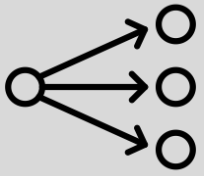
MULTIPLE EXAMPLES OF SYSTEMIC (ABSCOPAL) EFFECT

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

1: 8 patients had non-injected target lesions only, incl 2 patients with PR

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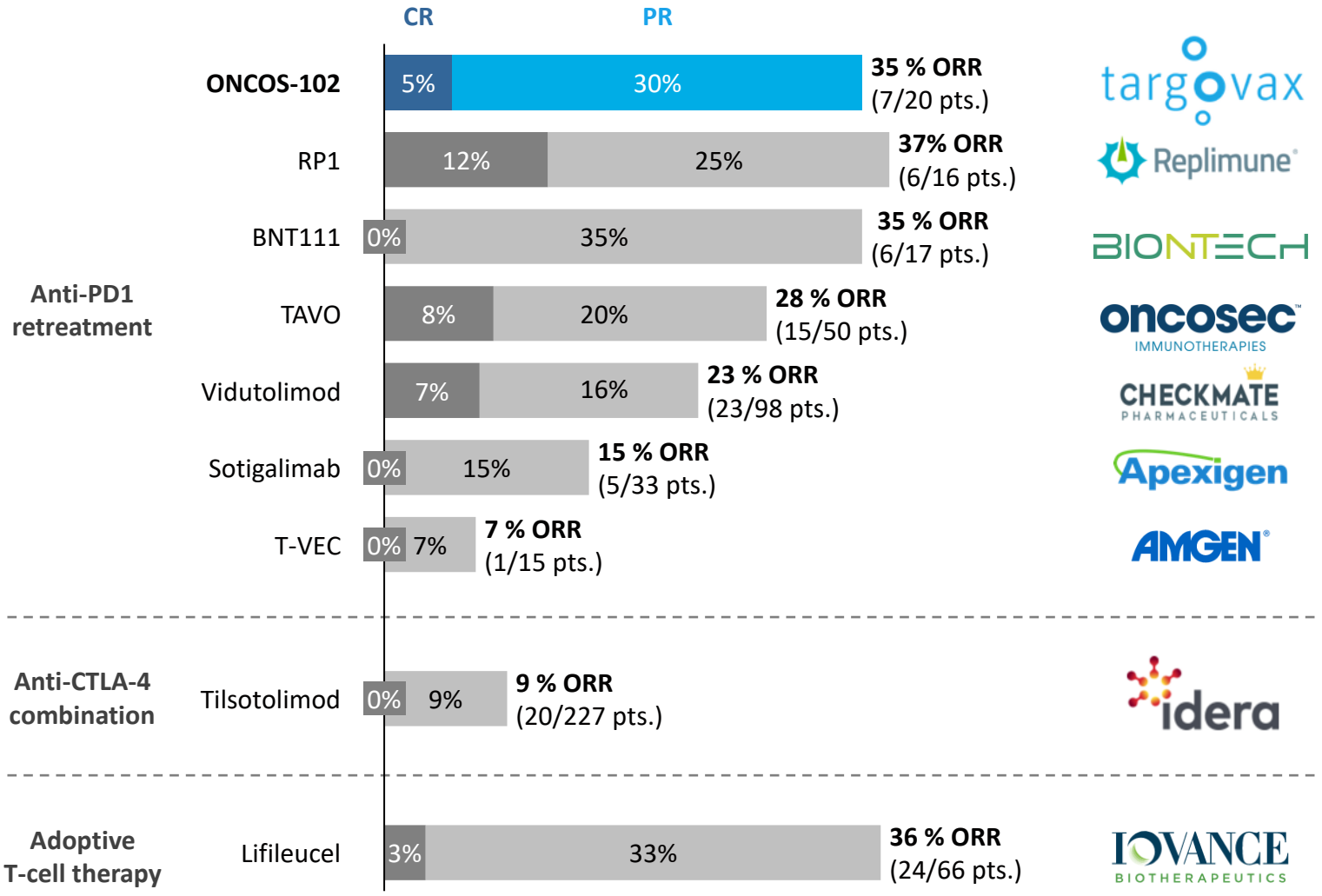
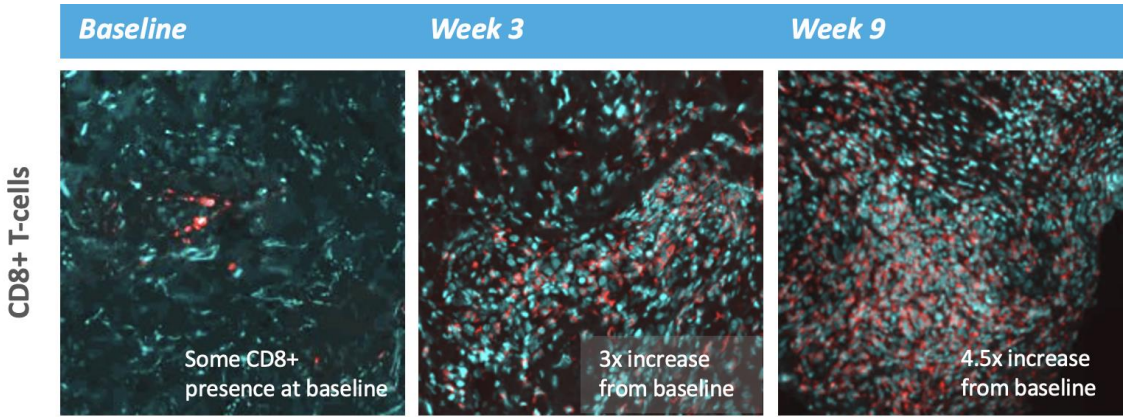
ONCOS-102 HAS DEMONSTRATED HIGHLY COMPETITIVE ORR OF 35% IN PD1 REFRACTORY MELANOMA



Targovax market analysis, June 2022

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

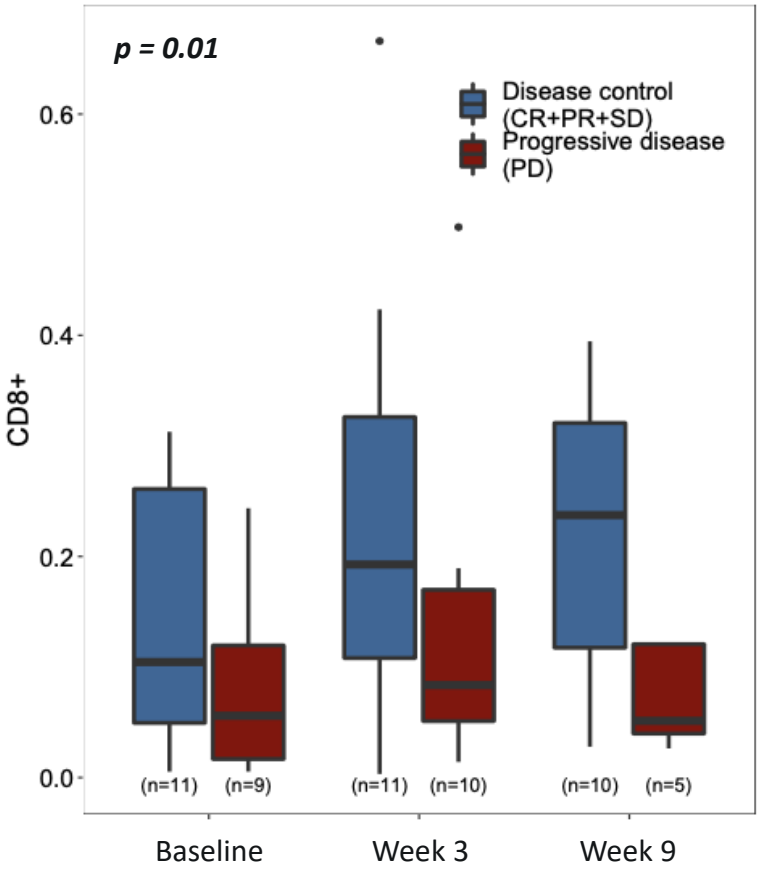
CD8+ T-cell tumor infiltration
Tumor biopsy IHC, patient case example



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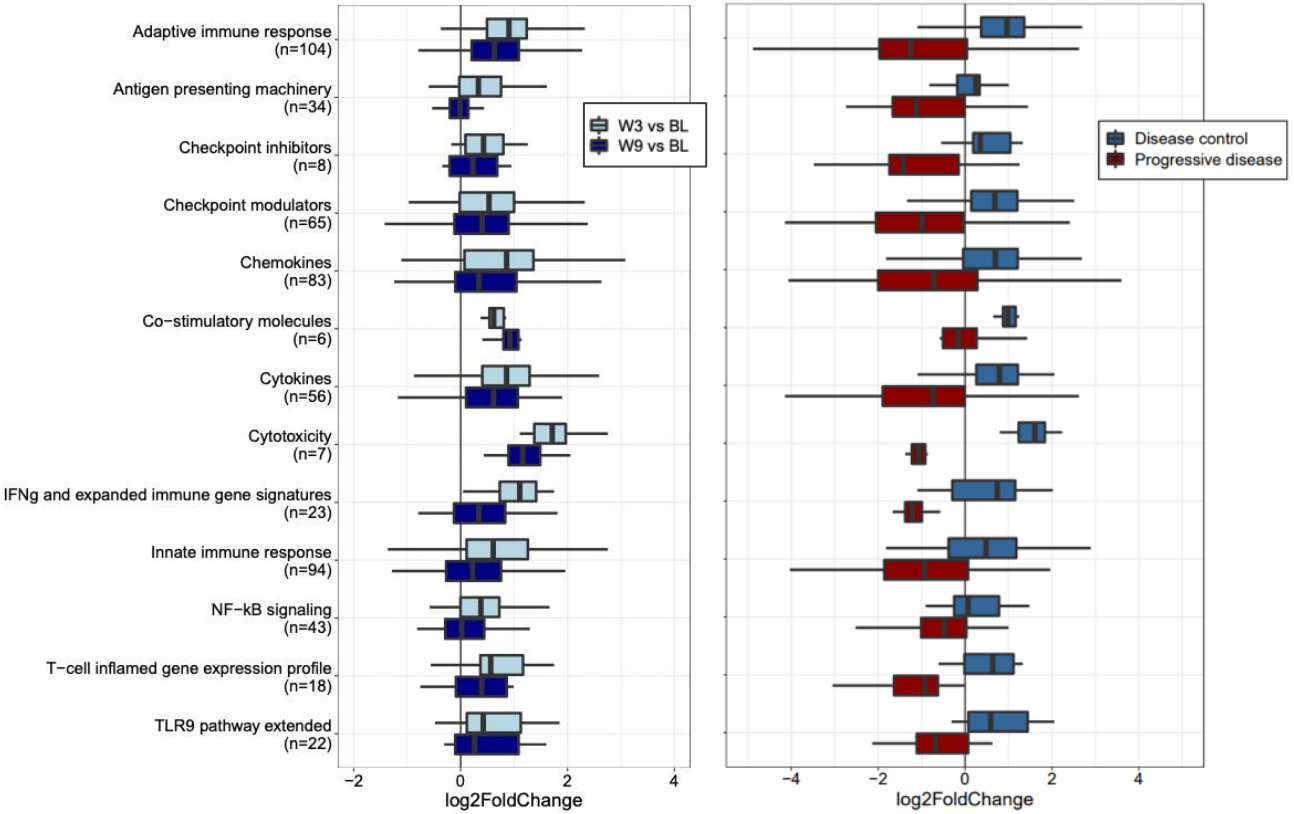
GENE EXPRESSION DATA CONFIRMS IHC OBSERVATIONS AND DETAILS BROAD PRO-INFLAMMATORY TUMOR RE-PROGRAMING

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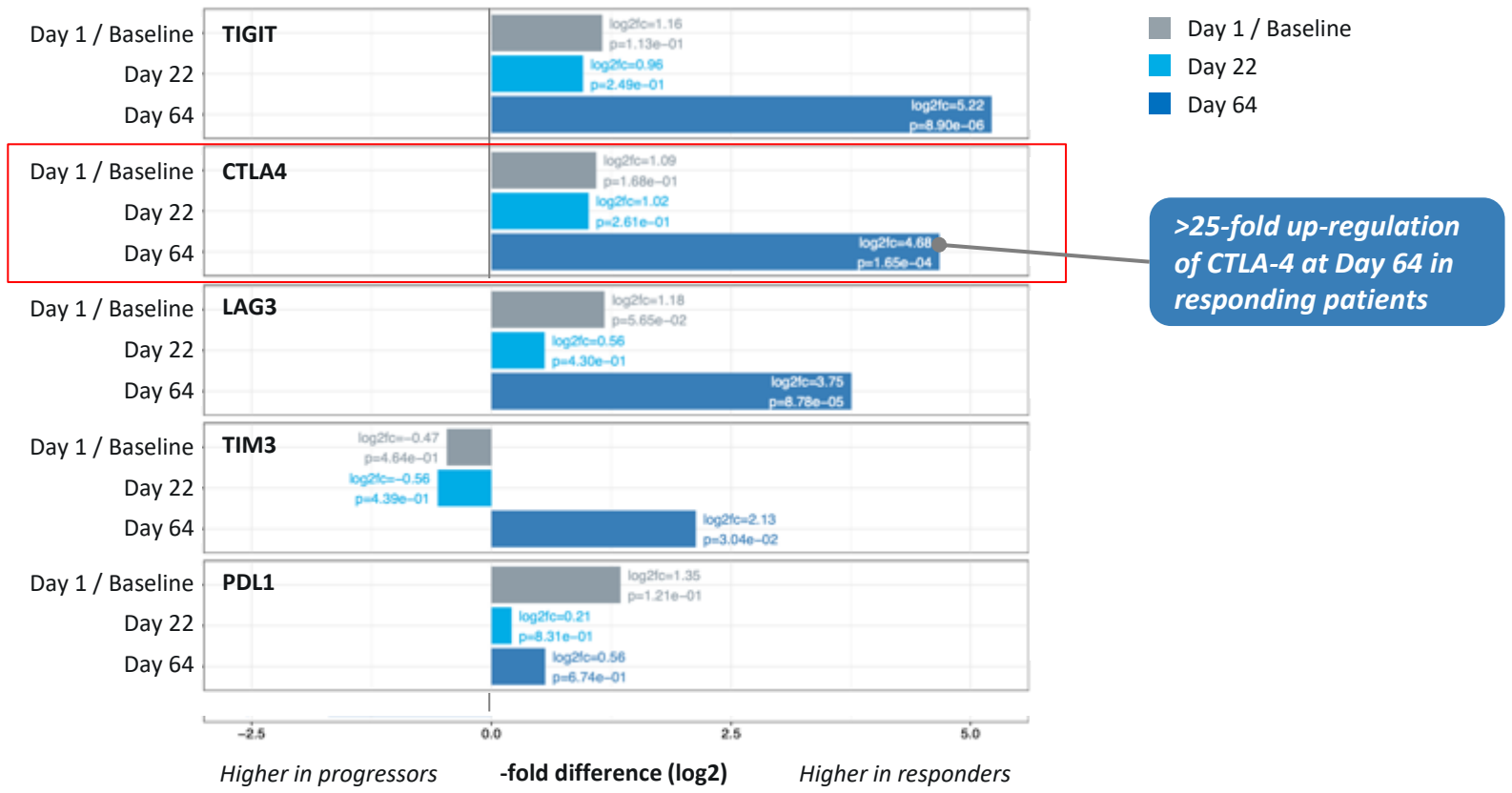
CTLA-4 IS STRONGLY UPREGULATED IN RESPONSE TO ONCOS-102 TREATMENT IN MELANOMA

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



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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

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

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

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

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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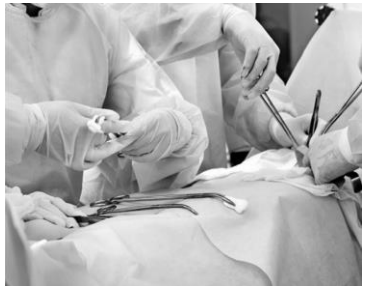
THERE IS A HIGH UNMET MEDICAL NEED IN MALIGNANT PLEURAL MESOTHELIOMA



Surgery

Only 10% of patients suitable for resection

Often diagnosed too late for surgery

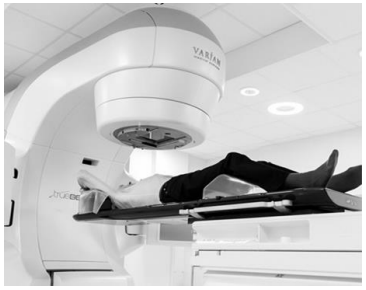
Technically challenging

Radiotherapy

Rarely effective due to tumor shape

Hard to focus radiation

Mainly palliative care



Chemotherapy

Standard of care (SoC) with limited efficacy

Pemetrexed/cisplatin only approved option until 2020

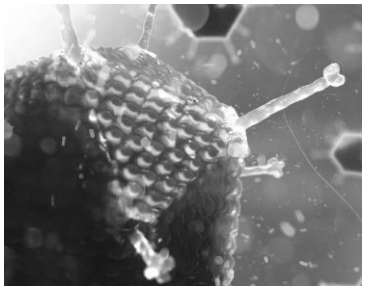
12-16 mo. mOS in 1L

Immunotherapy

Opdivo/Yervoy combination approved in 1L in 2020

Replacing chemotherapy as preferred first-line option in sarcomatoid patients

18 mo. mOS in 1L, high toxicity



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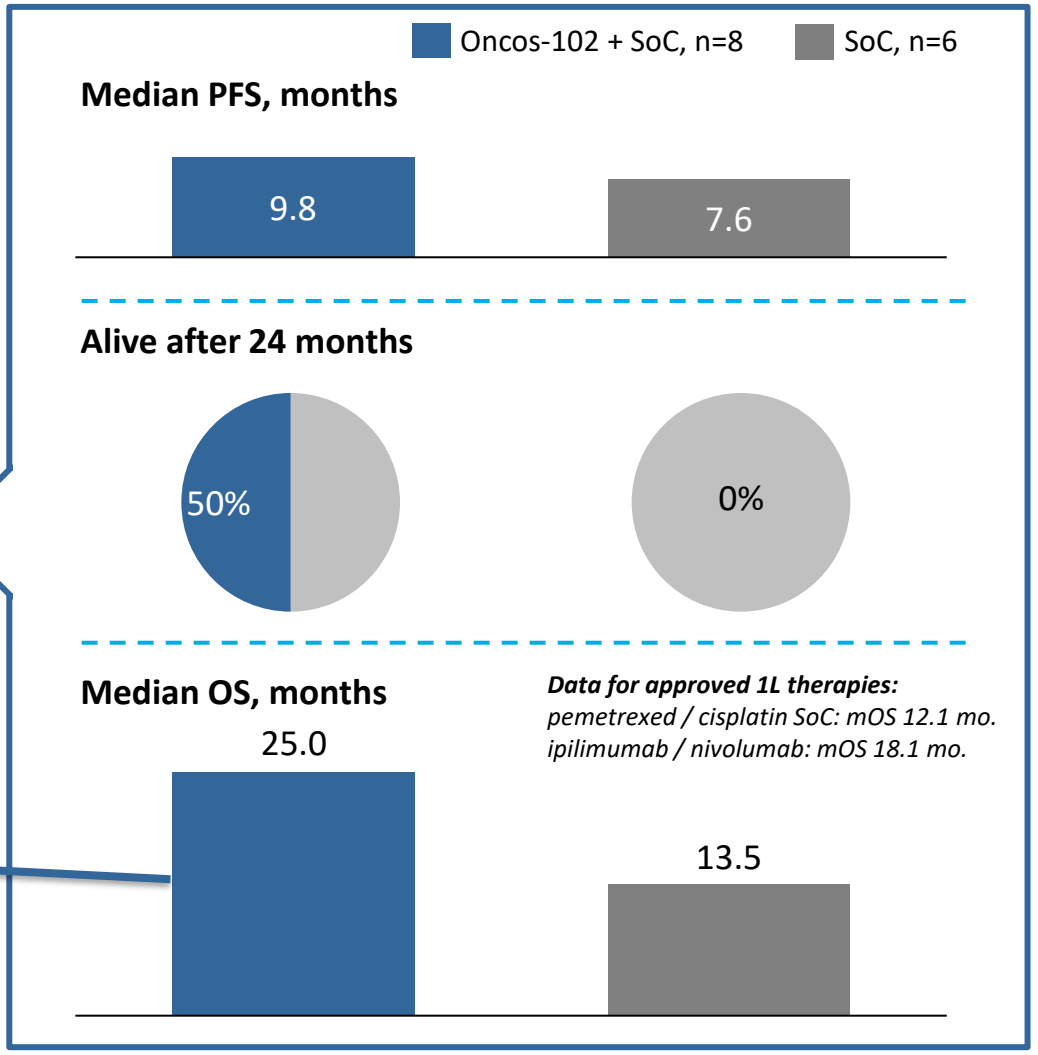
CLINICAL BENEFIT OF ONCOS-102 COMBINATION WITH CHEMOTHERAPY IN FRONT-LINE MESOTHELIOMA

Trial design

- 1st and 2nd (or later) line
- ONCOS-102: 6 intra-tumoral injections
- SoC chemo: pemetrexed and cisplatin, 6 cycles

	Safety lead-in n=6	Experi-mental n=14	Control n=11
Front line	3	8	6
Later line*	3	6	5



ONCOS-102 + SOC mOS compares well to ipilimumab/nivolumab 18.1 month mOS in phase 3 that lead to FDA approval late 2020

ONCOS-102 shows survival benefit even in the absence of checkpoint inhibition

* Second or later line treatment

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

mPFS when combining safety lead-in and randomized part in first line is 8.9 months

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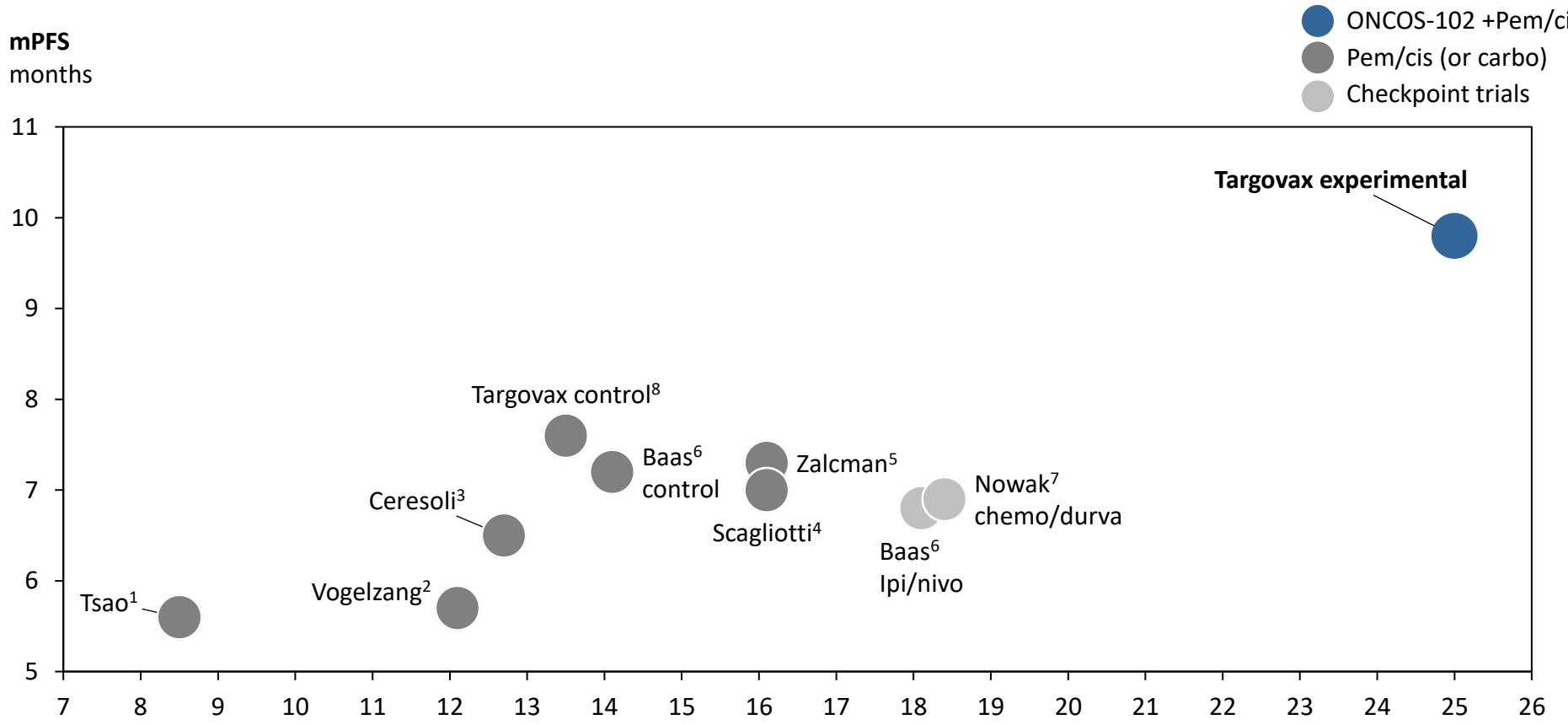
ONCOS-102 + CHEMOTHERAPY: 25 MONTHS mOS IN 1L MESOTHELIOMA, BEST SURVIVAL DATA REPORTED IN THIS POPULATION

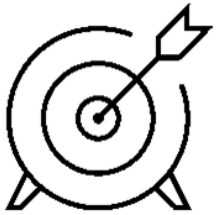


1 Tsao 2019 (JCO) compared cediranib + pem/cis vs pem/cis; data from pem/cis arm presented on plot
2 Vogelzang 2003 was the basis for FDA approval of pemetrexed.
3 Ceresoli 2006, Pemetrexed plus carboplatin
4 Scagliotti 2019 (Lancet) compared nintedanib + pem/cis vs pem/cis; data from pem/cis arm presented 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)

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

SUMMARY

- OV class is alive and kicking, over 500 OV programs reported
- There is no one OV, each family is different, findings cannot be generalized
- Even within a family, OVs are very different:
  - Genetic modifications creating new properties (infection, safety, selectivity)
  - Transgene selection (boost immune response, tumor cell killing)



- Deeper understanding of OV biology and targeted effects on tumors
- OVs are being tested in combination treatments, primarily I-O agents
- Some OV like ONCOS-102 have shown synergy with PD-1 and chemotherapy

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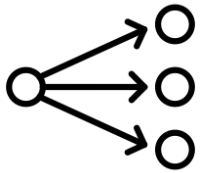

- Many clinical trials ongoing with data read out in late 2022 or 1H 2023
- Exciting times for OV developers and cancer patients

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Questions?

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