ONCOS-102: AN ADENOVIRUS BASED IMMUNE THERAPY IN SOLID TUMORS

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THERE IS A HIGH MEDICAL NEED FOR IMMUNE ACTIVATING AGENTS

Checkpoint inhibitors *are revolutionizing cancer therapy…*

…but ***minority of patients respond…***

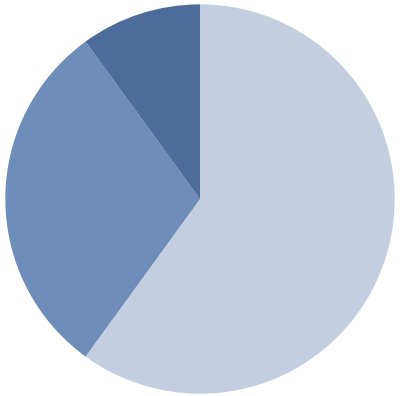
…leading to a ***high need for immune activators*** *to boost checkpoint response rates*

22 bn USD

Global CPI market[1]

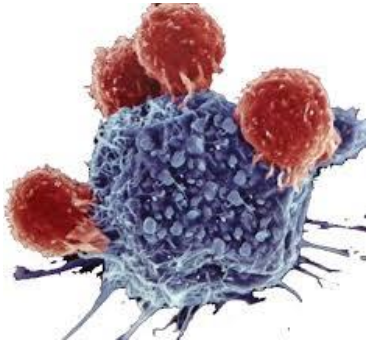
44 %

Patients eligible for CPI[2]:



10 - 40 %

Responders



[1] Immune Checkpoint Inhibitors Markets Report, 2020 January, ResearchAndMarkets.com

[2] Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs, JAMA Netw Open. 2019 May; 2(5), Haslam A., Prasad V.

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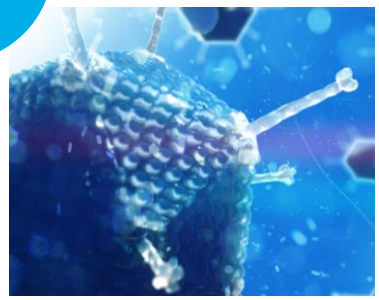
TARGOVAX'S FOCUS IS TO DEVELOP IMMUNE ACTIVATORS TO ENHANCE THE EFFECT OF CHECKPOINT INHIBITORS

Targovax focus



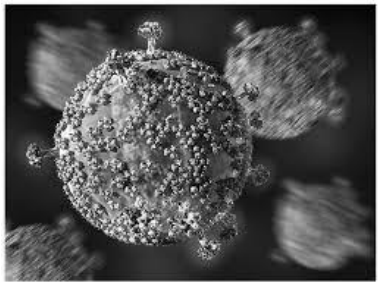
Immune activators

Oncolytic viruses, vaccines

Checkpoint inhibitors

PD1, PDL-1, CTLA-4

Surgery - Radio - Chemo

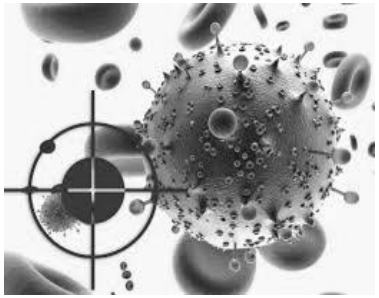


Cell therapies

CAR-Ts, TCRs

Targeted therapy

TKIs, PARPs, etc.



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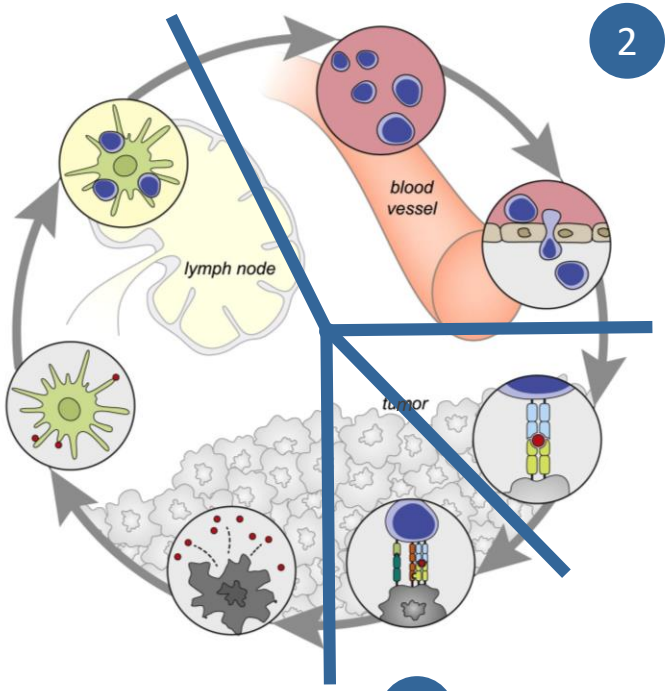
FOUR CRITICAL COMPONENTS OF IMMUNE ACTIVATION

1 Access to tumor antigens, cross-presentation by APCs and priming of T-cells



2 T-cell migration and infiltration into the tumor

3 Expansion and survival of T-cells in the tumor

4 Tumor cell recognition and elimination

Adapted from Chen & Mellman, Immunity 2013

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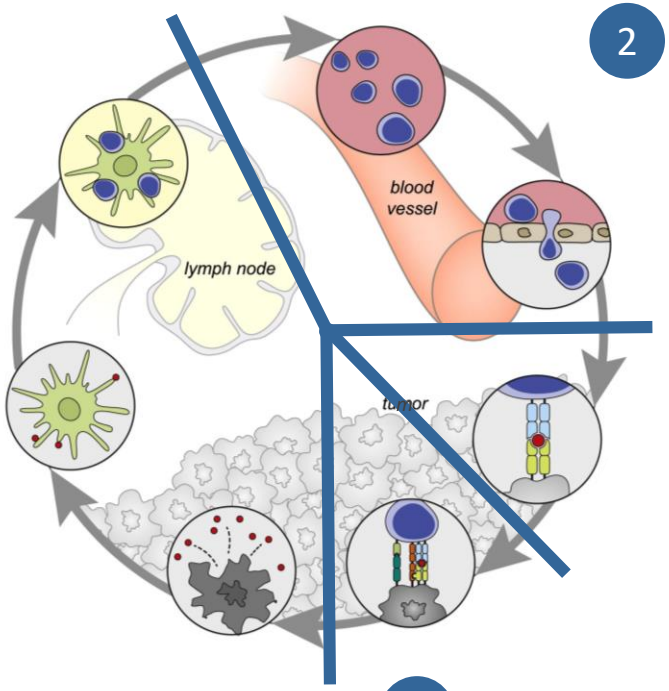
RESISTANCE TO CHECKPOINT INHIBITION

1 Access to tumor antigens, cross-presentation by APCs and priming of T-cells

Problem: *Low tumor immunogenicity and ineffective T-cell priming*



2 T-cell migration and infiltration into the tumor

Problem: *T-cells do not reach the tumor*

3 Expansion and survival of T-cells in the tumor

Problem: *Exhaustion of T-cells in the tumor*

4 Tumor cell recognition and elimination

Problem: *Immunosuppression in the tumor*

Adapted from Chen & Mellman, Immunity 2013

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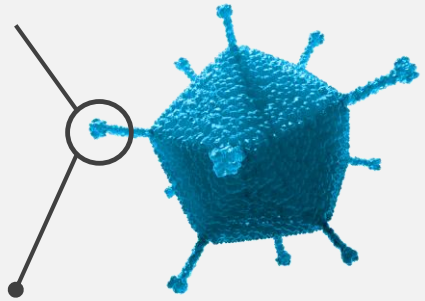
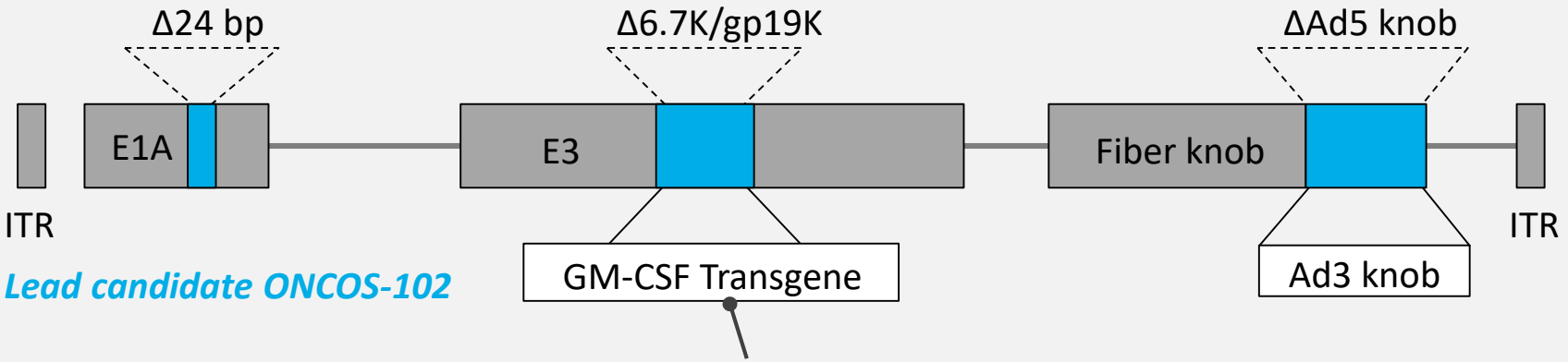
THE ONCOS ONCOLYTIC VIRUS HAS BEEN ENGINEERED TO PROVIDE SOLUTIONS TO PROBLEMS OF RESISTANCE

Selective replication in cancer cells

Boosting the **immune activation**

Enhanced infection of cancer cells





Lead candidate ONCOS-102

DNA insertion site *– opportunity to deliver genetic payload of choice*

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SOLUTION 1: ONCOS-102 DRIVES DANGER SIGNALLING AND INDUCES T-CELL PRIMING

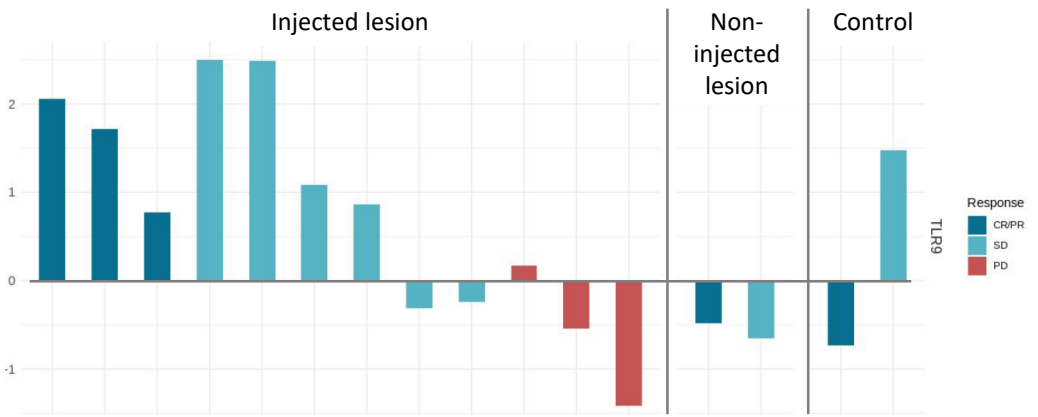
Underlying causes

- Lack of neoantigens and/or poor neoantigen fitness
- Failure to activate danger signals

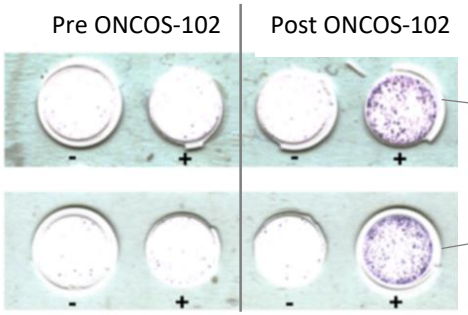
Impact of ONCOS

- Upregulation of TLR9 expression
- Induction of tumour antigen specific T-cells

TLR9 signaling in tumor RNAseq -fold change D36 vs. baseline[1], mesothelioma



Tumor-specific T-cells IFNγ Elispot assay, patient case examples[2]



- Example - anti-Mesothelin; MAGE-A1, MAGE-A3 and NY-ESO-1 also detected
- NY-ESO-1 present at 17 mo. follow-up

- Example - anti-MAGE-A3
- Present also at 6 mo. follow-up

1 Unpublished company data
2 Ranki et al. JITC 2016

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SOLUTION 2: ROBUST INCREASE IN T-CELL TUMOR INFILTRATION FOLLOWING ONCOS-102 TREATMENT

Underlying causes

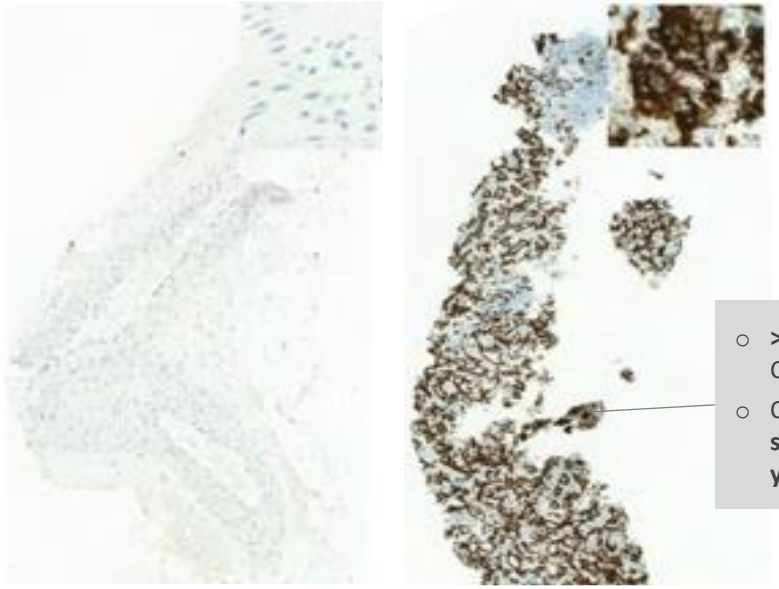
- Production of CXCL12 by stromal fibroblasts
- Trapping of T-cells in stroma

Impact of ONCOS

- Upregulation of several chemokines
- T-cell infiltration in response to virus injection

ONCOS-102 induced tumor T-cell infiltration
Ovarian cancer patient case example, monotherapy

Tumor biopsy mIHC – CD8+ T-cells



- **>1000-fold increase** of CD8+ T-cells in tumor
- Ovarian cancer patient – **stable disease for three years**

Pre-treatment
Baseline

Post-treatment
Week 8

Ranki et al. JITC 2016

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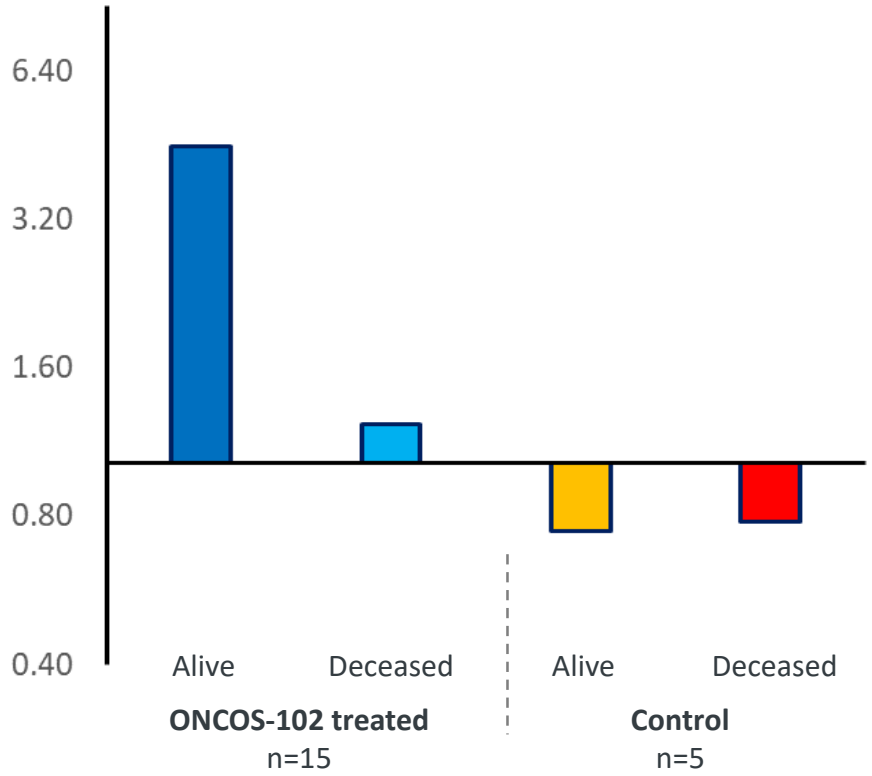
ONCOS-102 PROMOTES PD-L1 UPREGULATION IN THE TUMOR

PD-L1 upregulation in mesothelioma tumors at day 36
Fold change, ONCOS-102 treated vs. untreated



*

Unpublished company data
* Control patients treated with standard-of-care chemotherapy

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SOLUTION 3: ONCOS-102 TREATMENT DRIVES SHIFT TOWARDS HIGHER RATIO OF CYTOTOXIC T-CELLS

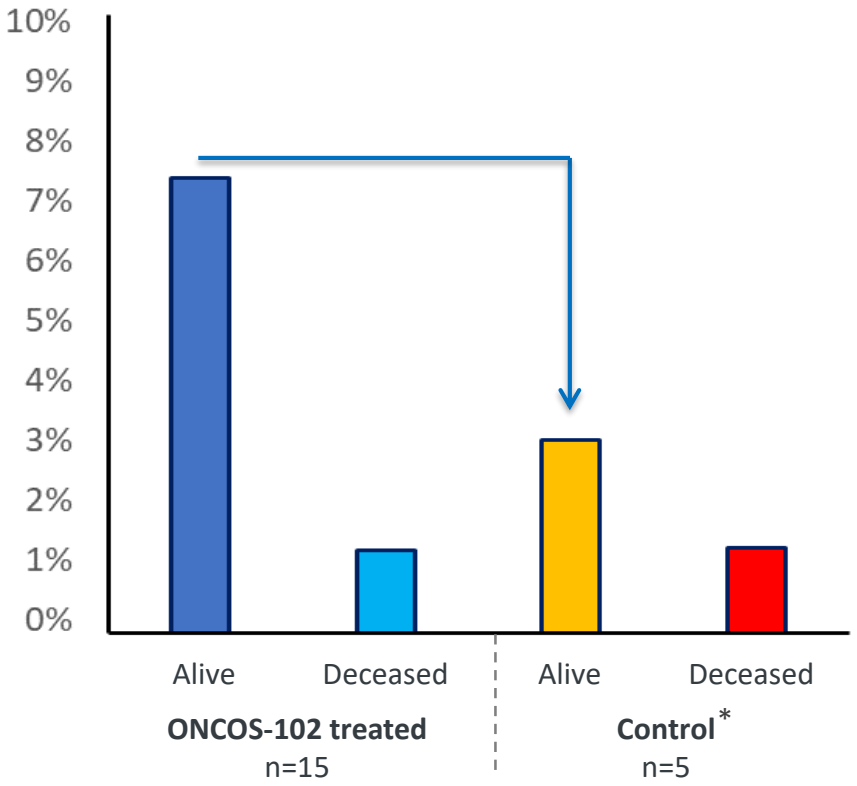
Underlying causes

- Low expression of co-stimulatory molecules and pro-inflammatory cytokines
- Co-expression of multiple co-inhibitory receptors by T-cells

Impact of ONCOS

- Up-regulation of several co-stimulators and pro-inflammatory cytokines, such as IFNγ
- Increased fraction of intra-tumoral cytotoxic T-cells

Relative level of cytotoxic GrB+ / CD8+ T-cells at day 36
Alive vs. deceased at 12 months, mesothelioma



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Unpublished company data
* Control patients treated with standard-of-care chemotherapy

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SOLUTION 4: ONCOS-102 INDUCES POLARIZATION TOWARDS INFLAMMATORY M1 MACROPHAGES

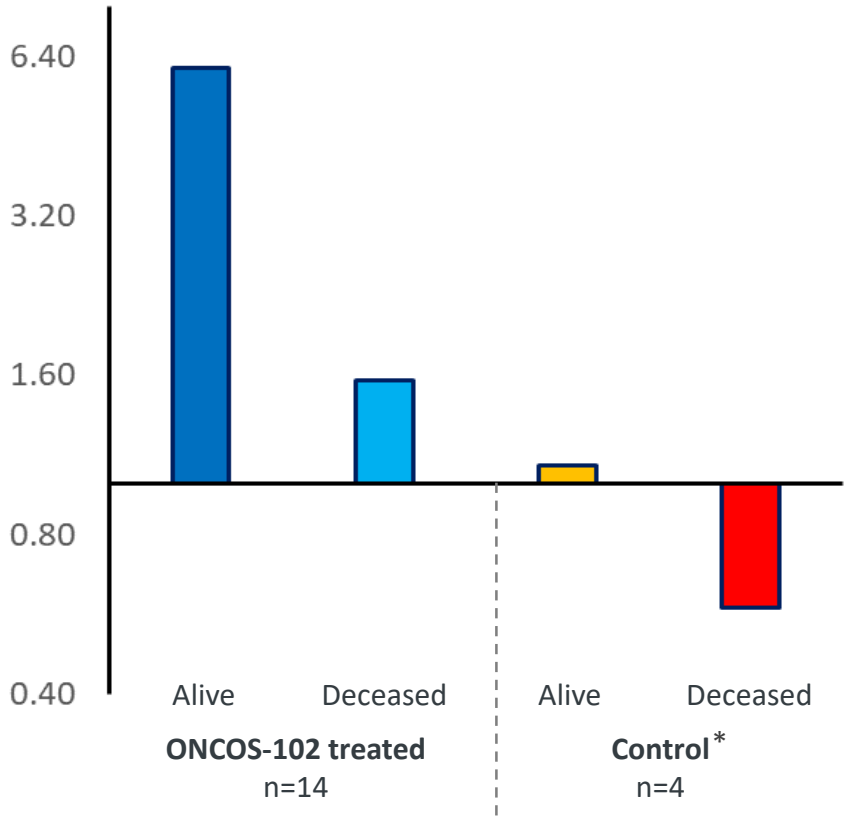
Underlying causes

- Increased level of inhibitory myeloid cells, such as M2 macrophages
- Induction of inhibitory regulatory T-cells

Impact of ONCOS

- Shift towards inflammatory immune cell population
- Polarization of M2 to M1 macrophage phenotype

M1 vs. M2 macrophage ratio in tumors at day 36
Alive vs. deceased at 12 months, mesothelioma



Unpublished company data
* Control patients treated with standard-of-care chemotherapy

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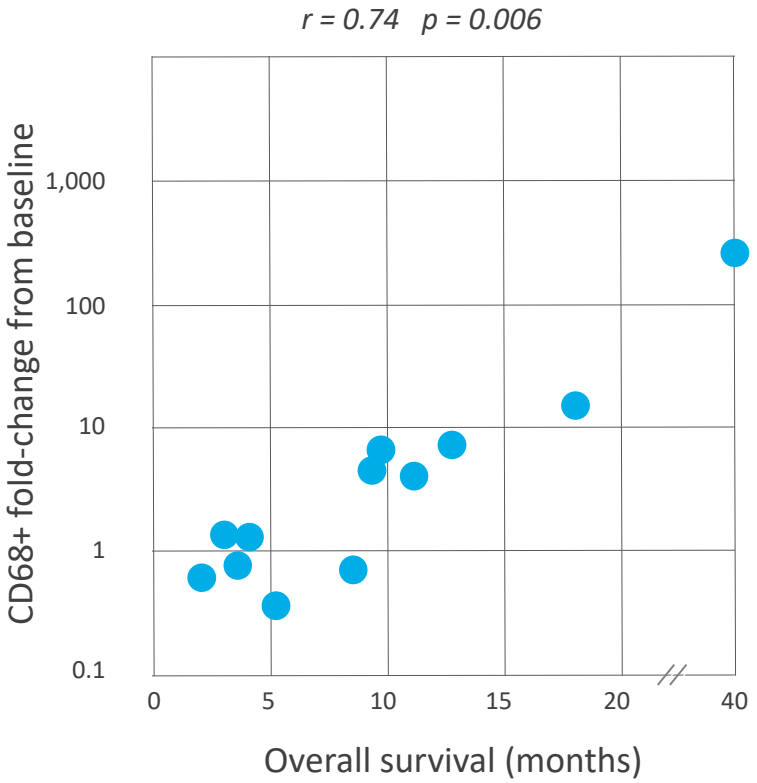
INFLAMMATORY MODULATION LINKED TO SURVIVAL (MONOTHERAPY)

Fold-change CD68+ macrophages vs. survival
Intra-tumoral, ONCOS-102 monotherapy



 Ranki et al, JITC 2016

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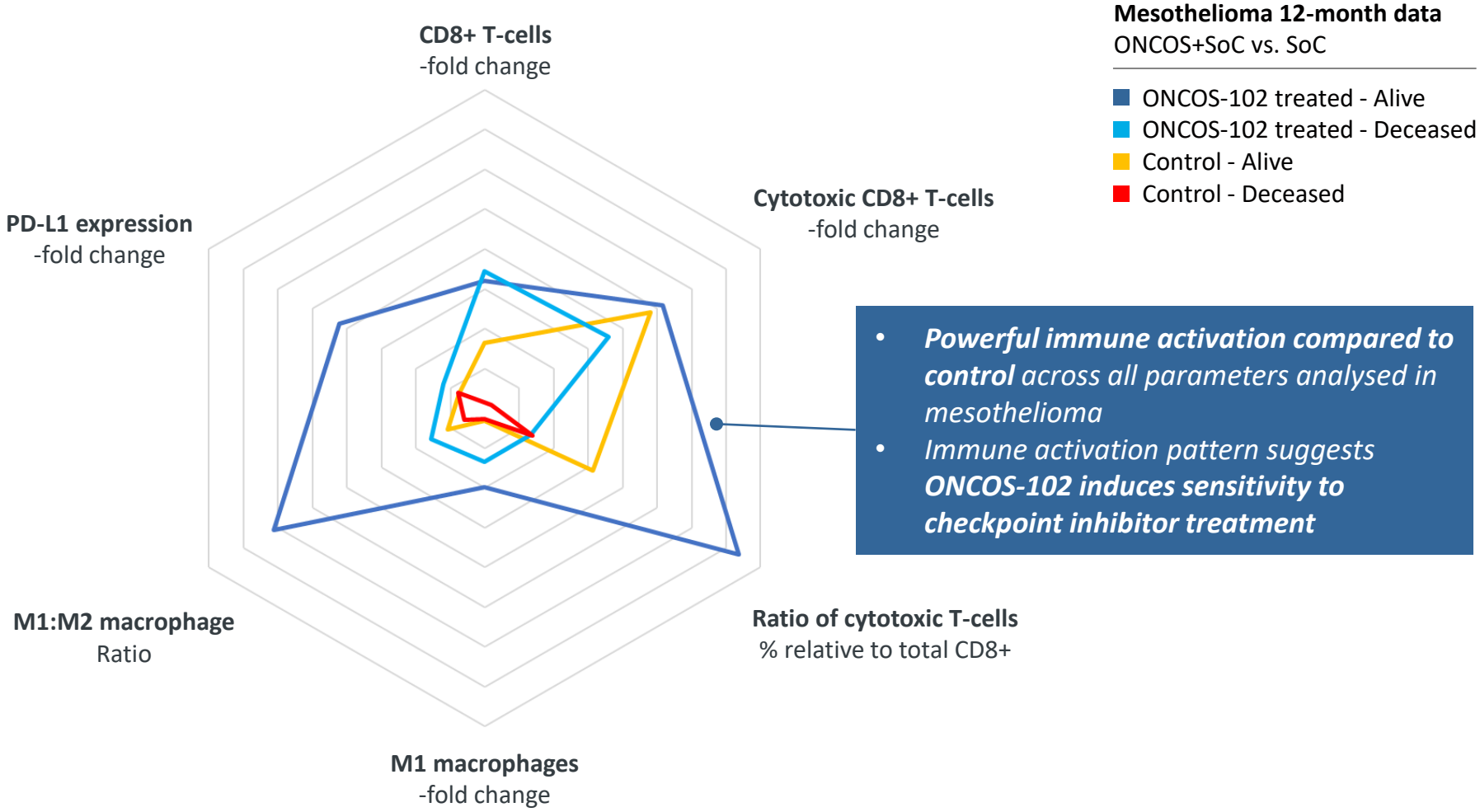
BROAD IMMUNE ACTIVATION IS LINKED TO CLINICAL BENEFIT (WITH CHEMO)



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

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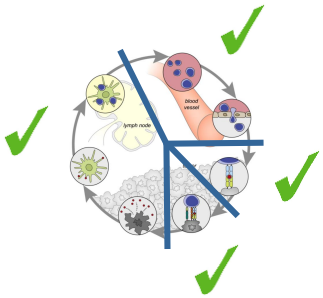
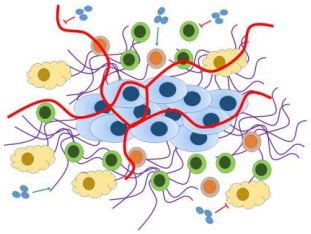
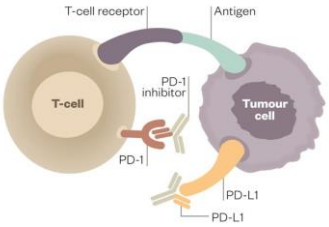
ONCOS-102 IMMUNE ACTIVATION - CONCLUSIONS



ONCOS-102 activates the immune system and counteracts multiple mechanisms of immuno-suppression operating at different steps of the cancer immunity cycle



Modulation of the tumor micro-environment is linked to clinical benefit in patients with different tumor types



Immune activation provides **broad and powerful priming to sensitize patients** to respond to subsequent treatment with **checkpoint inhibitors**

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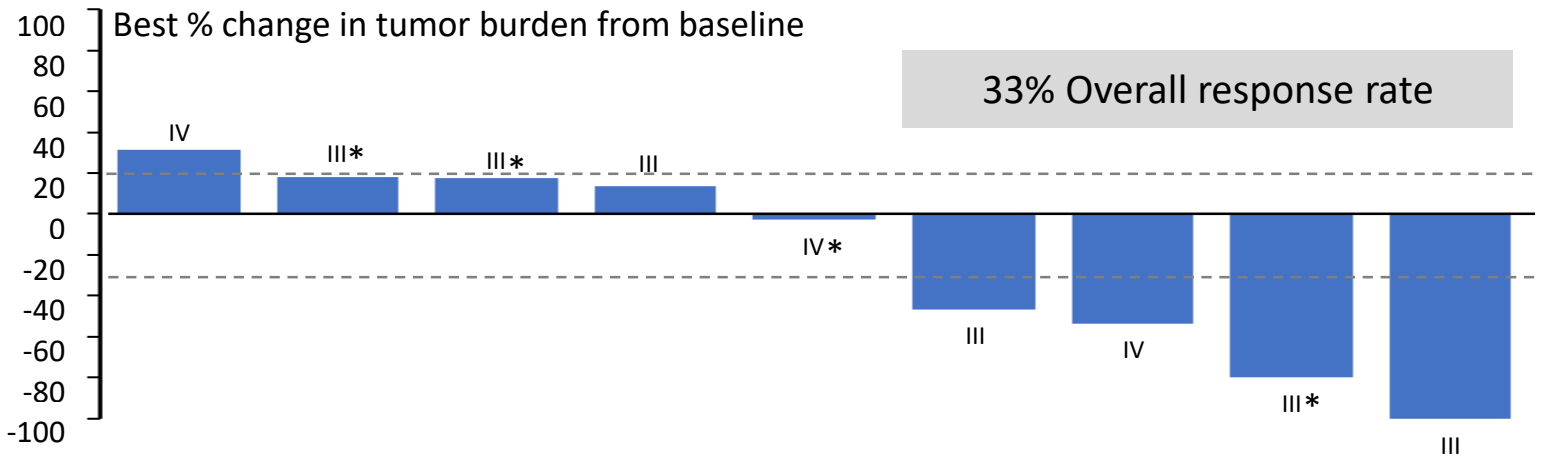
DEVELOPMENT PROGRAM

Product candidate	Preclinical	Phase I	Phase II	Collaborator	Next expected event
ONCOS-102	**Mesothelioma** Combination w/ pemetrexed/cisplatin			MERCK	**2H 2020** Survival data
	Melanoma Combination w/Keytruda				**2H 2020** Part 2 clinical data
	Colorectal Combination w/Imfinzi			AstraZeneca CANCER RESEARCH INSTITUTE	*Update by collaborator*
	Prostate Combination w/DCvac			sotio	*Update by collaborator*
ONCOS-200 series	**Next Gen viruses**			leidos	*Updates at conferences*
Novel mutRAS concepts				VALO THERAPEUTICS OBLIQUE THERAPEUTICS	

ONCOS-102 + KEYTRUDA IN ANTI-PD1 REFRACTORY MELANOMA

PROMISING OUTCOME IN FIRST NINE PATIENTS

Tumor reduction in target lesions



33% Overall response rate

Case example: Early and durable complete response (CR)

Stage IIIb, Prior therapies

- Surgery x 3
- Yervoy
- Dabrafenib + Trametinib
- Keytruda

Baseline: Progression on Keytruda

Week 3: 3x ONCOS-102 only

Week 9: 3x ONCOS-102 & 2x Keytruda

* Non-target progression / new lesion (PD)
Letters and numbers indicating disease stage
Preliminary data presented at SITC 2019

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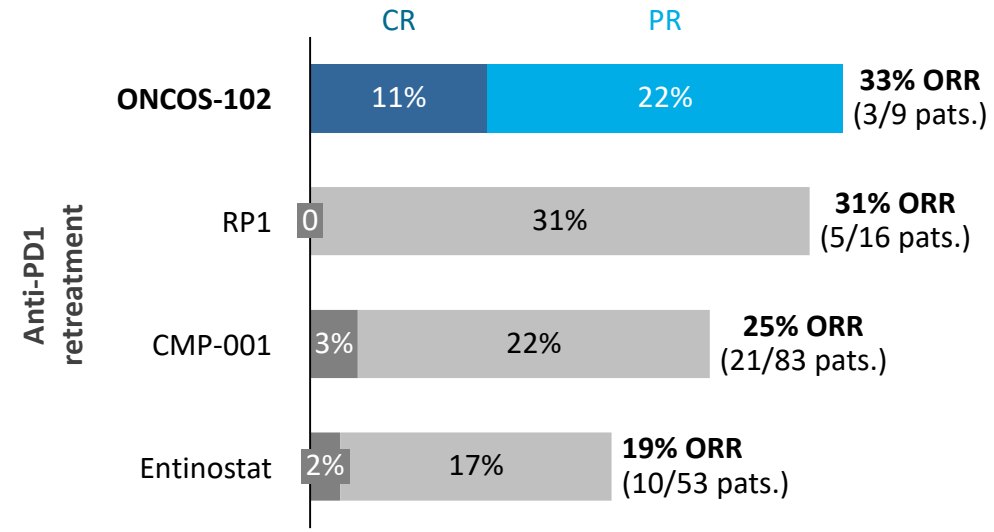
ONCOS-102 HAS PRODUCED EFFICACY DATA COMPETITIVE TO LEADING DRUG CANDIDATES IN PD1 REFRACTORY MELANOMA



Comment

- targovax
  - *Adenovirus expressing GM-CSF*
- Replimune
  - *Herpesvirus expressing GM-CSF and GALV*
- CHECKMATE PHARMACEUTICALS
  - *TLR-9 agonist*
  - *Data from high dose cohort*
- Syndax
  - *HDAC inhibitor*

CTLA4 naïve, 10-20% ORR expected

- MERCK
  - *Coxsackievirus, no transgene*
- idera
  - *TLR-9 agonist*
- IOVANCE BIOTHERAPEUTICS
  - *Autologous TIL therapy with IL-2*
  - *Complex and expensive manufacturing*

SOURCE: Targovax market analysis, May 2020

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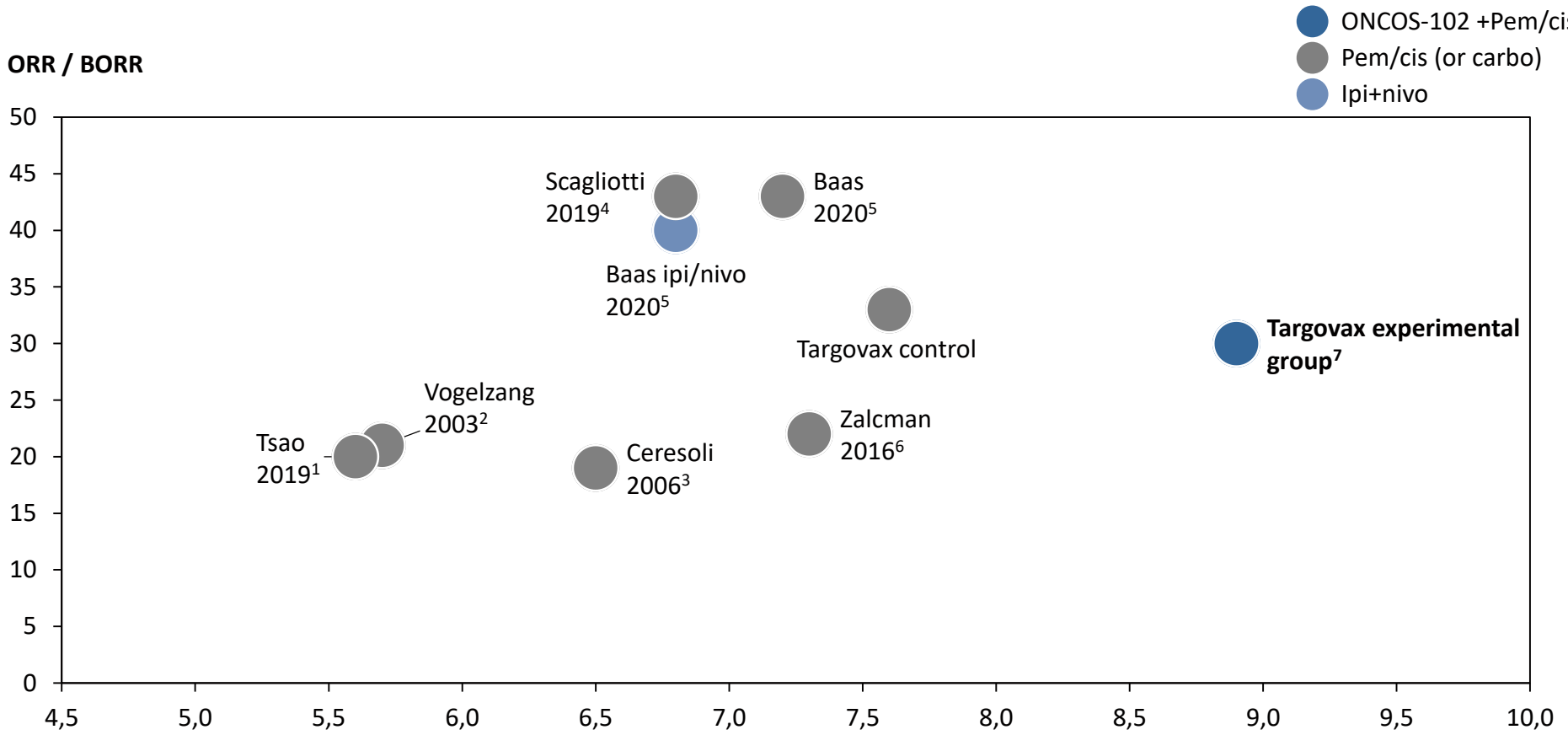
CLINICAL BENEFIT IS ALSO DEMONSTRATED IN MESOTHELIOMA

ONCOS-102 COMBINED WITH CHEMO VS CHEMO ALONE IN FIRST LINE



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. FDA review disputed originally reported data, reducing confirmed BORR to 21% (Hazarika 2005)
3 Pemetrexed plus carboplatin, BORR
4 Scagliotti 2019 (Lancet) compared nintedanib + pem/cis vs pem/cis; data from pem/cis arm presented on plot
5 Baas 2020 CheckMate 743. Nivolumab + ipilimumab for two years vs pem/cis (or carboplatin) for 6 months
6 Zalcman 2016 (Lancet) compared bevacizumab + pem/cis vs pem/cis; data from pem/cis arm presented on plot. Not specified if ORR or BORR.
7 mPFS may change: Experimental group 11 patients (3 censored)

ORR: Overall Response Rate. BORR: Best Overall Response Rate

ACTIVATING THE PATIENT'S IMMUNE SYSTEM

TO FIGHT CANCER

BEST-IN-CLASS IMMUNE ACTIVATION

ONCOS-102 has clinically demonstrated the broadest and most powerful immune activation of any oncolytic virus, both as monotherapy and in combinations

ENCOURAGING CLINICAL EFFICACY

This powerful immune activation translates into clinical benefit for patients, in combination with both checkpoint inhibitors and chemotherapy