



ACTIVATING THE PATIENT'S IMMUNE SYSTEM TO FIGHT CANCER

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Immuno-Oncology Summit

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targovax

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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...

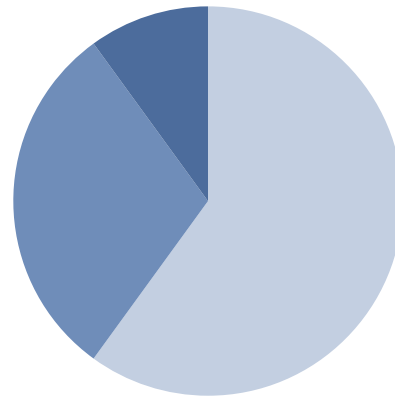
...leading to a high need for immune activators to boost checkpoint response rates

22 bn USD

Global CPI market¹

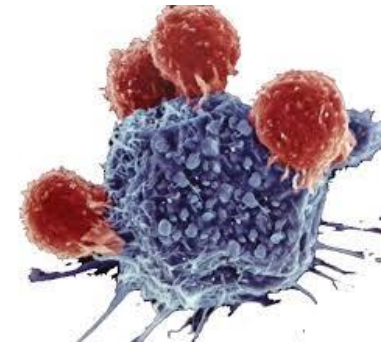
44 %

Patients eligible for CPI²:



10 - 40 %

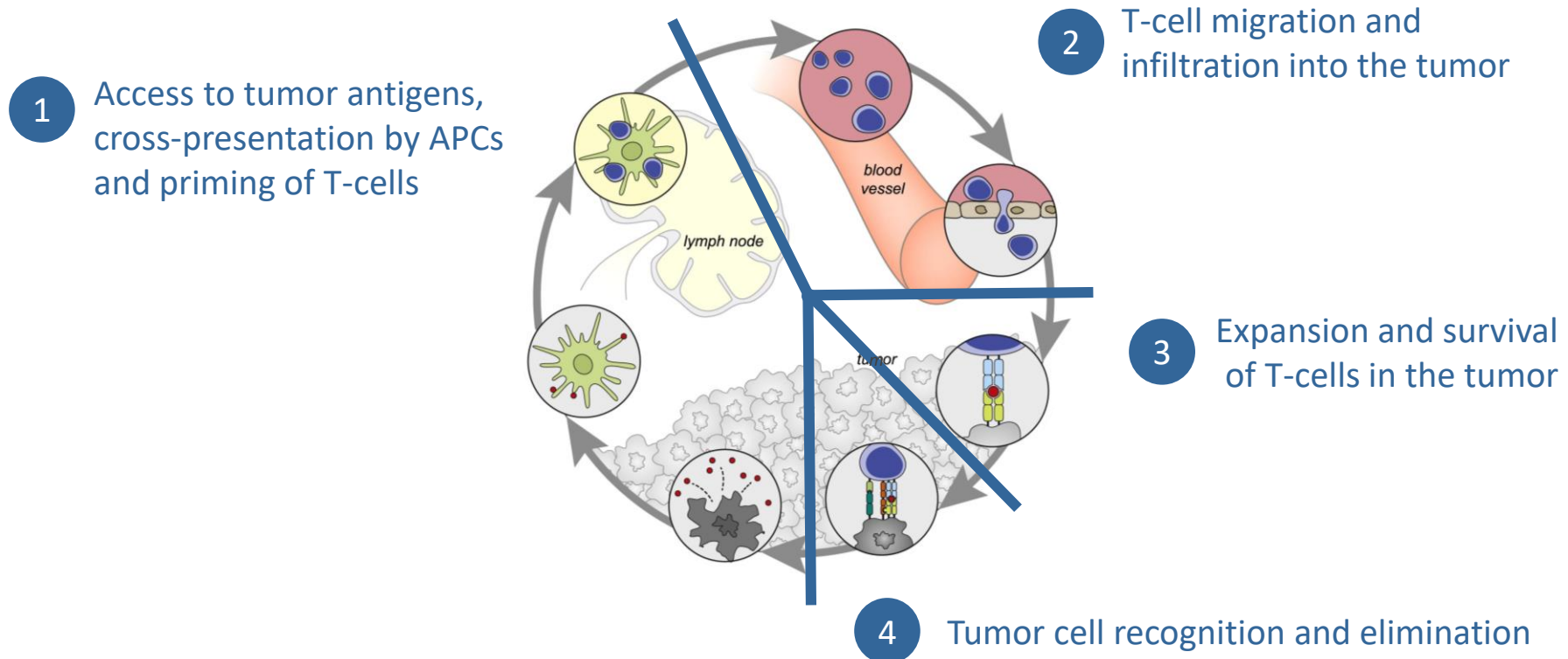
Responders



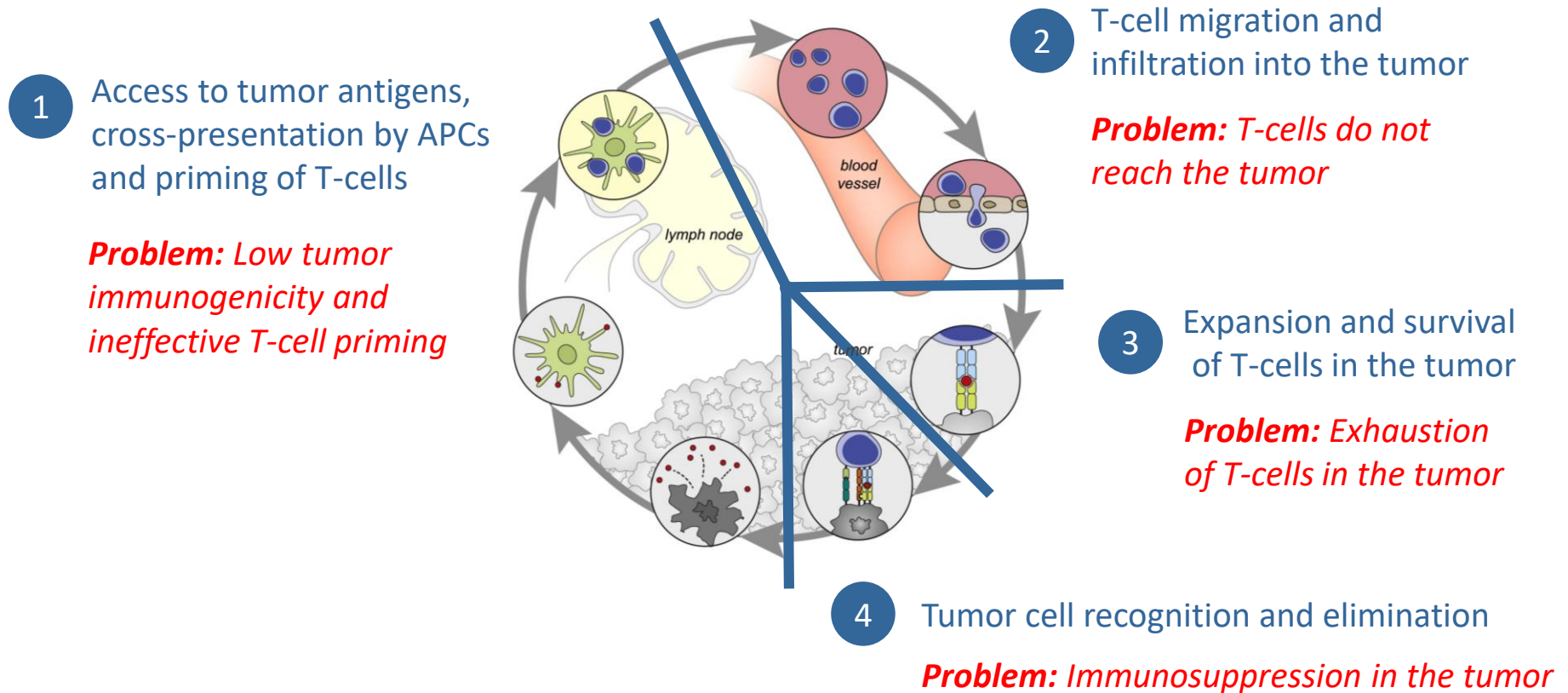
¹ Immune Checkpoint Inhibitors Markets Report, 2020 January, ResearchAndMarkets.com

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.

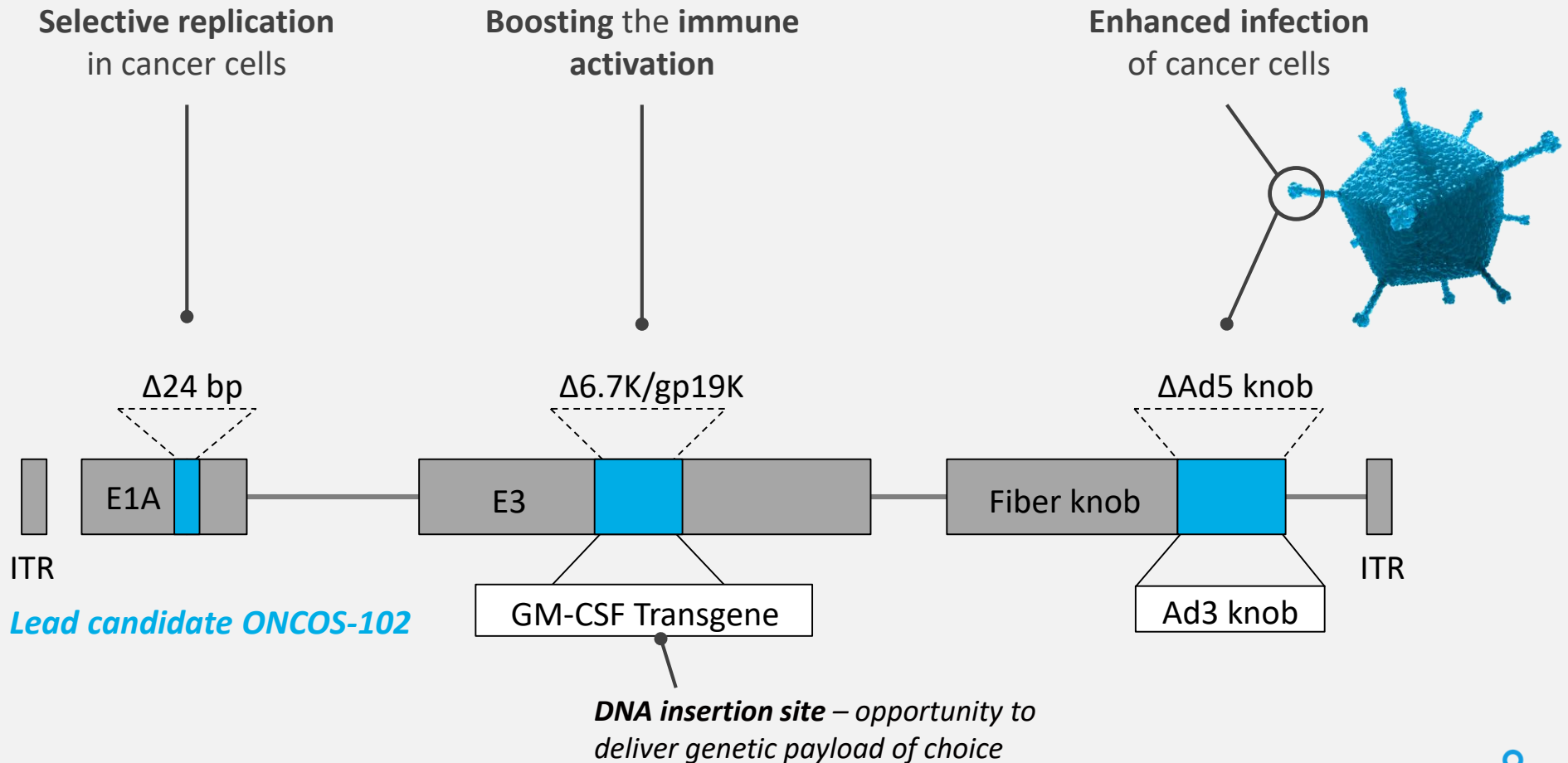
FOUR CRITICAL COMPONENTS OF IMMUNE ACTIVATION DRIVE THE RESPONSE TO IMMUNOTHERAPY

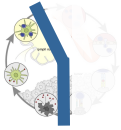


THESE COMPONENTS MALFUNCTION IN PATIENTS RESISTANT TO CHECKPOINT INHIBITION



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





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

Low tumor immunogenicity and ineffective T-cell priming

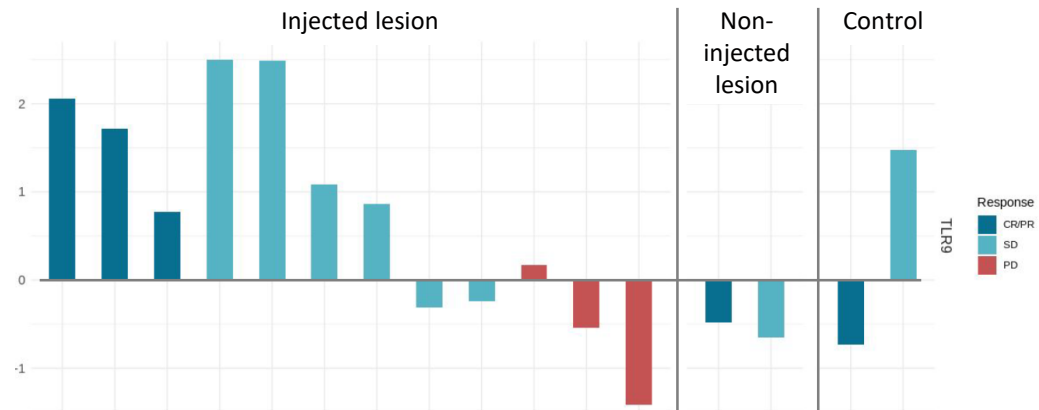
Underlying causes

- Lack of neoantigens and/or poor neoantigen fitness
- Insufficient dendritic cell activation
- Failure to activate danger signals

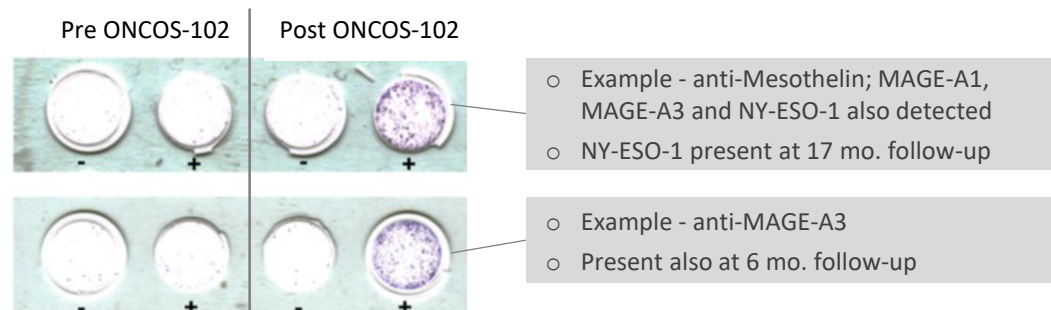
Impact of ONCOS

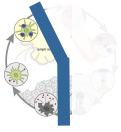
- Release and processing of tumor antigens through oncolysis
- Enhanced maturation of dendritic cells through GM-CSF expression
- Upregulation of TLR9 expression

TLR9 signaling in tumor RNAseq -fold change D36 vs. baseline¹, mesothelioma



Tumor-specific T-cells IFN γ Elispot assay, patient case examples²

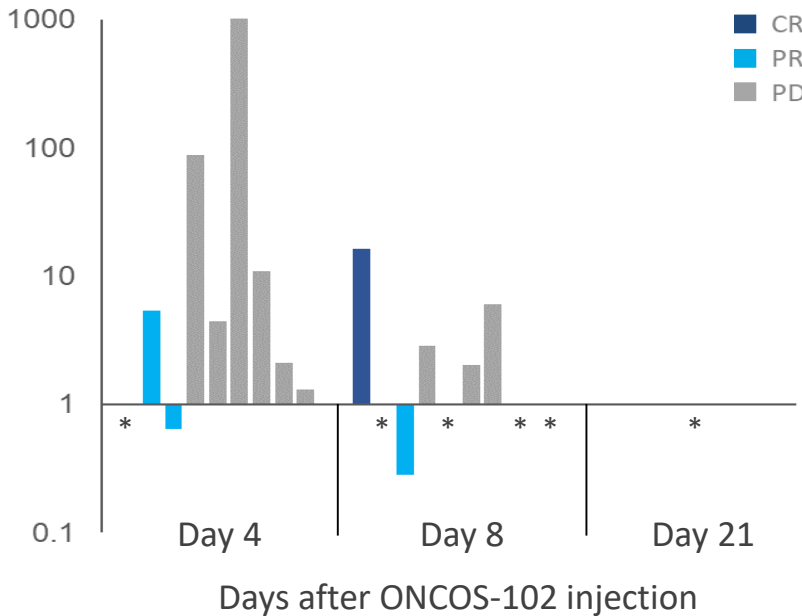




ONCOS-102 PRODUCES GM-CSF TO ENHANCE ANTI-CANCER T-CELL PRIMING AND EXPANSION

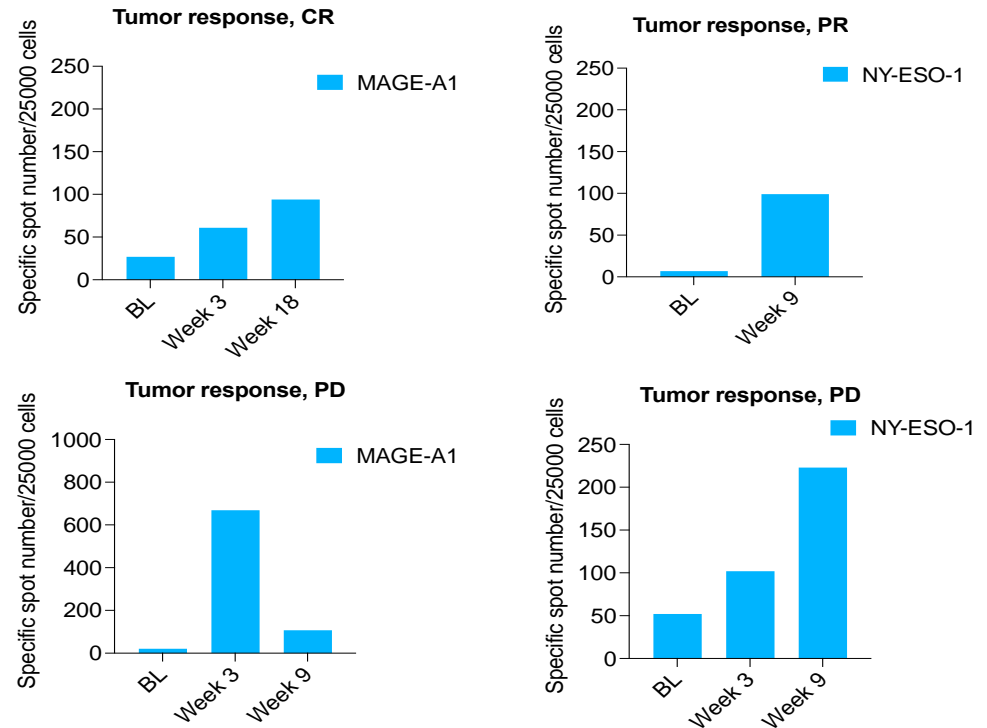
Systemic GM-CSF expression

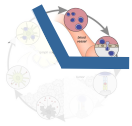
Fold change from baseline, PD1 refractory melanoma¹



Induction of systemic tumor antigen specific T-cells

IFN γ ELISPOT assay, PD1 refractory melanoma¹





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

T-cells do not reach the tumor

Underlying causes

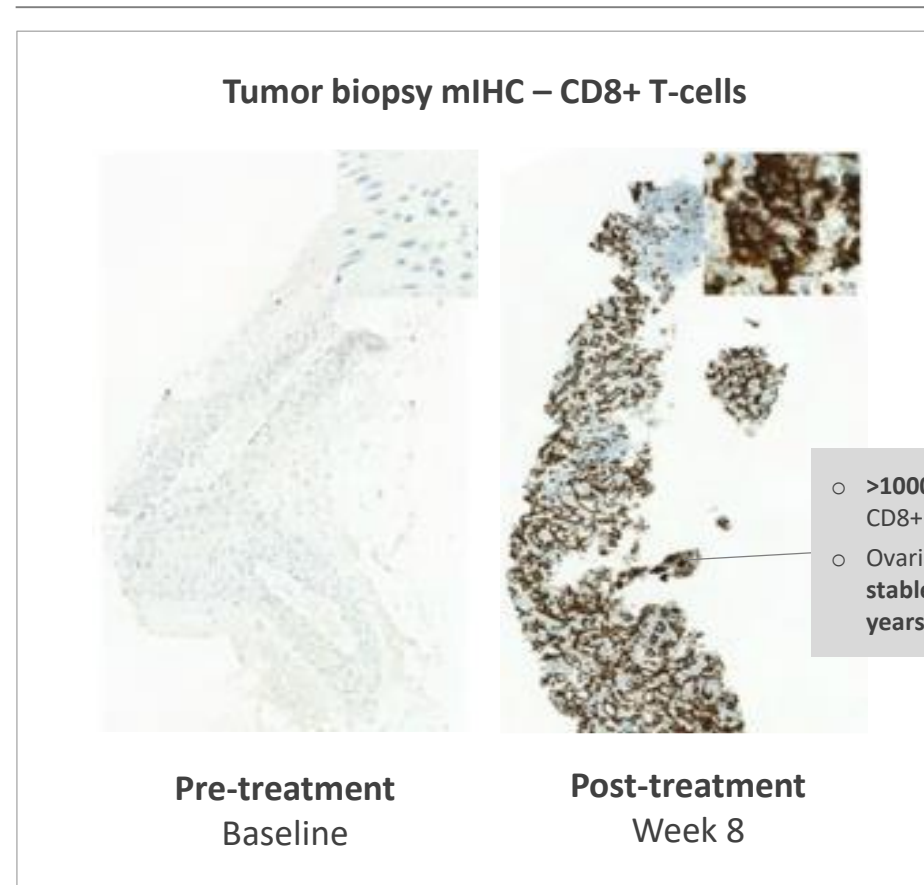
- Upregulation of WNT signaling and CCL4 suppression
- Production of CXCL12 by stromal fibroblasts
- Trapping of T-cells in stroma

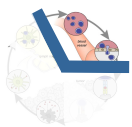
Impact of ONCOS

- Upregulation of several chemokines
- T-cell infiltration in response to virus injection
- Shift in T-cell localization from stroma to epithelium

ONCOS-102 induced tumor T-cell infiltration

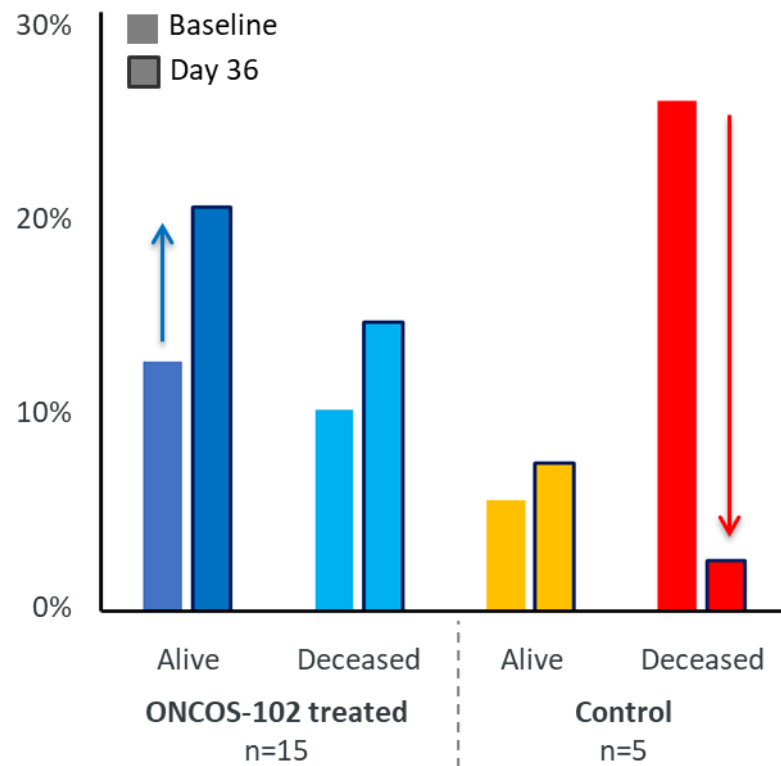
Ovarian cancer patient case example, monotherapy



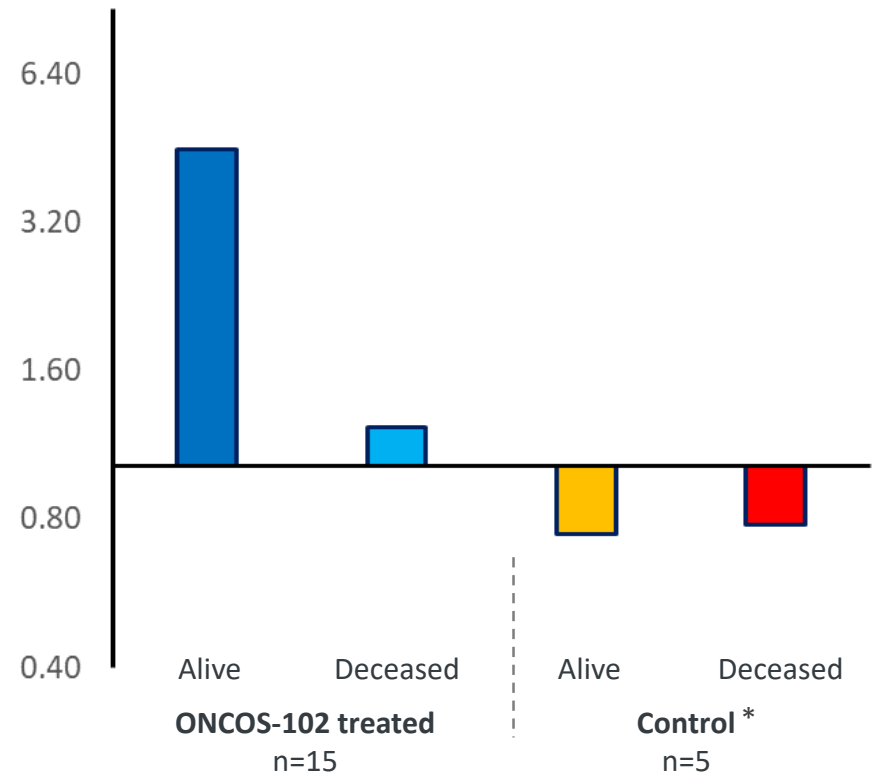


ONCOS-102 PROMOTES T-CELL INFILTRATION AND SUBSEQUENT PD-L1 UPREGULATION IN THE TUMOR

CD8+ T-cell tumor infiltration, % of cells
Alive vs. deceased at 12 months, mesothelioma



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





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

Exhaustion of T-cells in the tumor

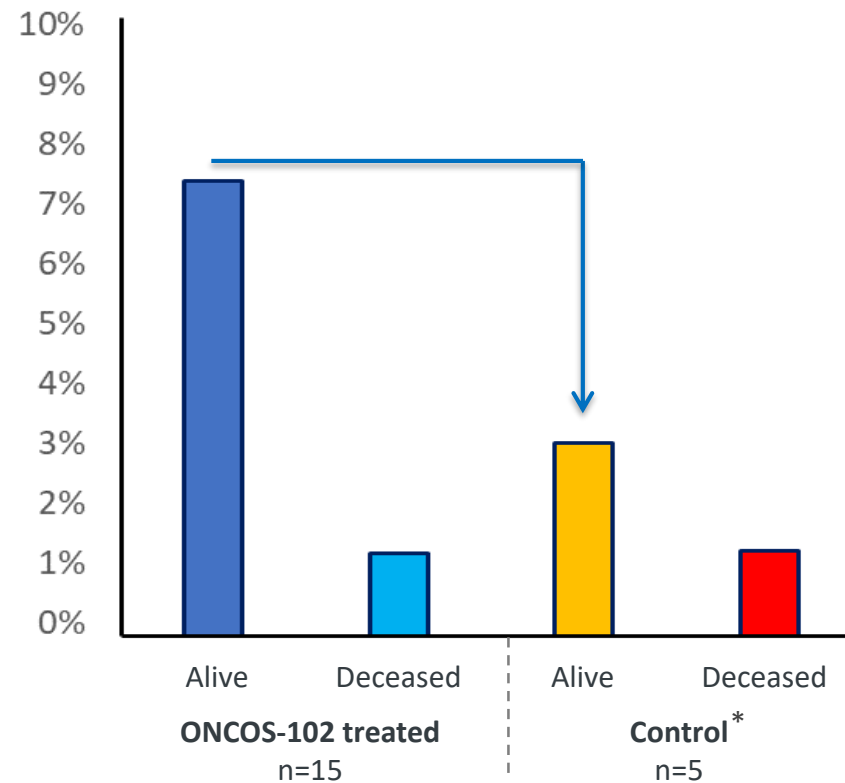
Underlying causes

- Continuous exposure of cancer-specific T-cells to tumor antigens
- 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 IFN γ
- 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

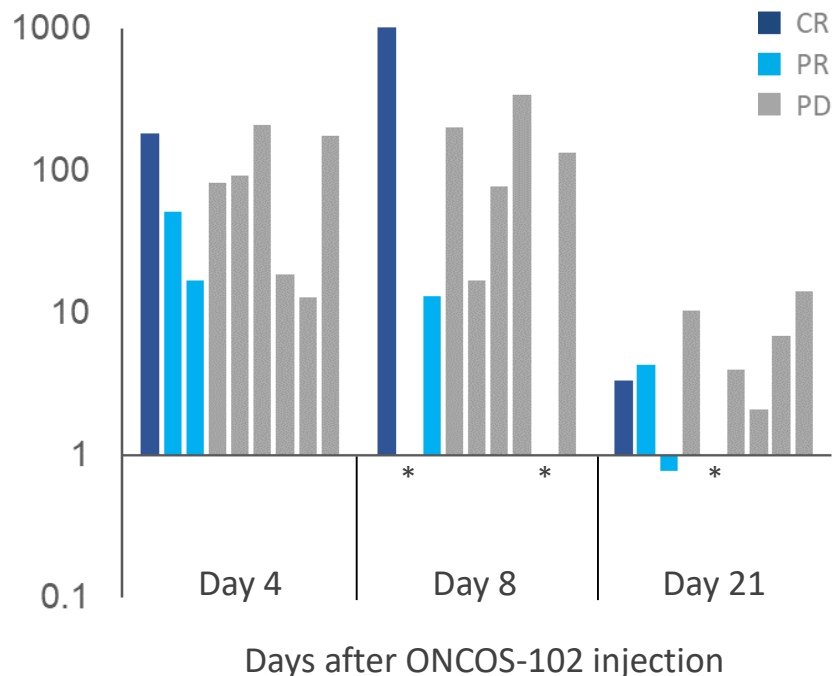




ONCOS-102 OUTPERFORMS CHEMOTHERAPY IN DRIVING LOCAL AND SYSTEMIC PRO-INFLAMMATORY SIGNALING

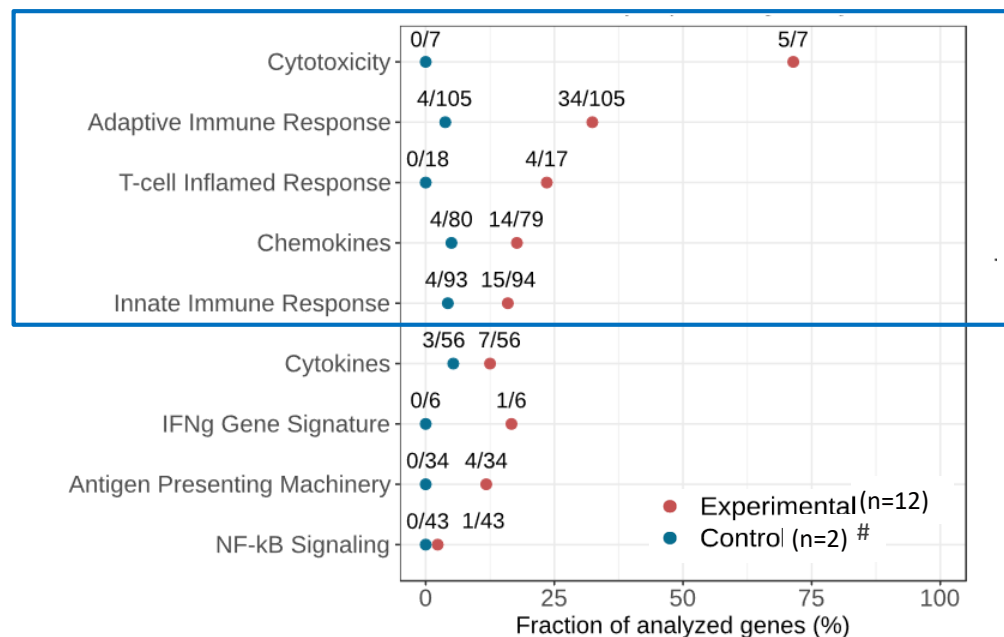
Systemic IFN γ expression

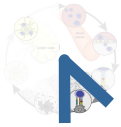
Fold change from baseline, PD1 refractory melanoma



Modulation of tumor gene expression, Fraction of genes

ONCOS-102 treated vs. untreated, mesothelioma





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

Immunosuppression in the tumor

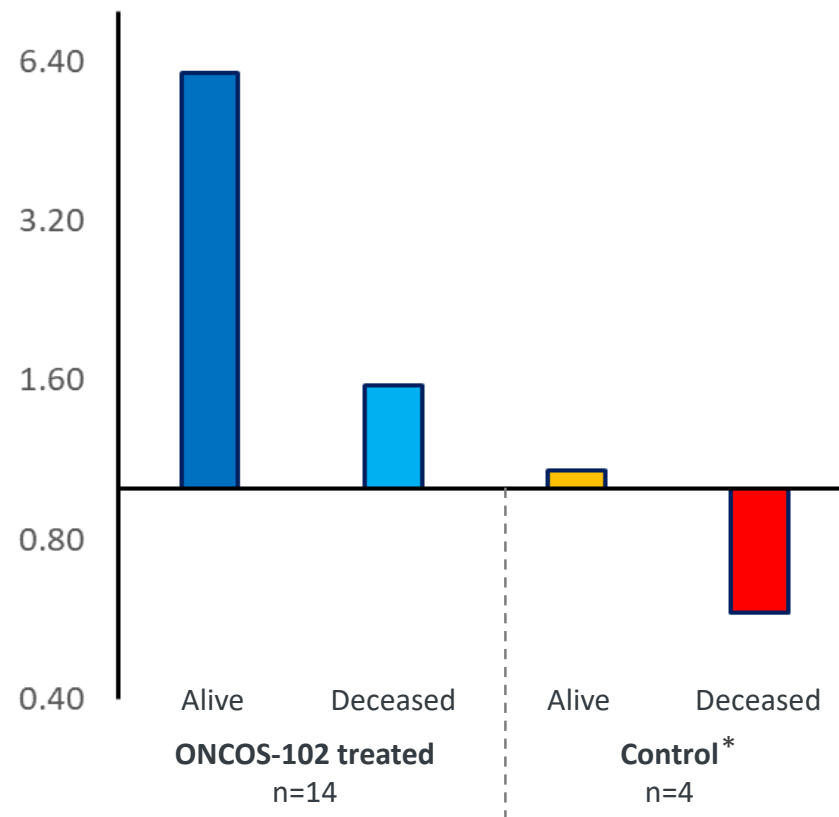
Underlying causes

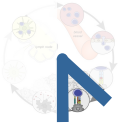
- Increased level of inhibitory myeloid cells, such as M2 macrophages and MDSCs
- Induction of inhibitory regulatory T-cells
- Various metabolic cues triggers as high local tumor adenosine generation to suppress T cells

Impact of ONCOS

- Induction of pro-inflammatory cytokine signaling, e.g. IL6
- 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

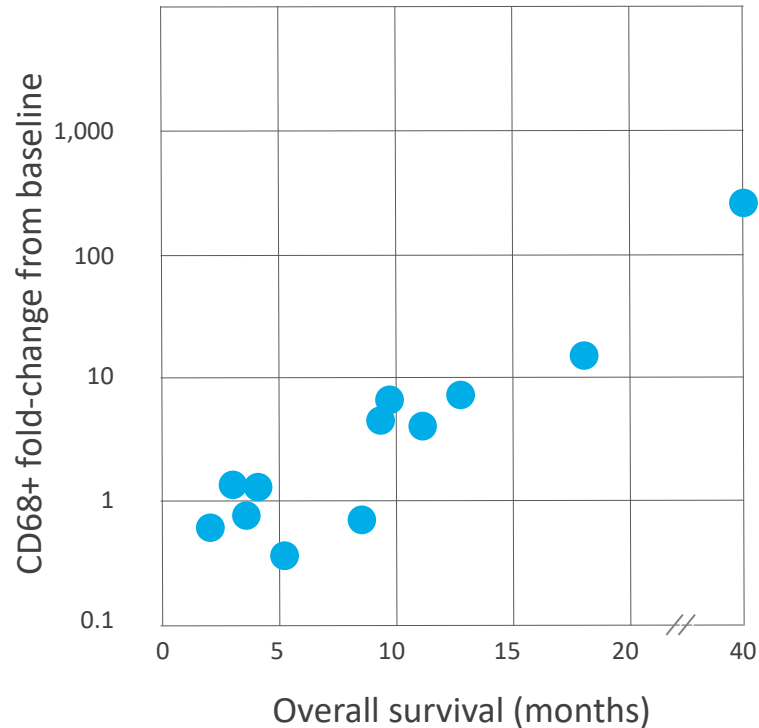




ONCOS-102 PROMOTES PRO-INFLAMMATORY MODULATION OF THE IMMUNE CELL INFILTRATE

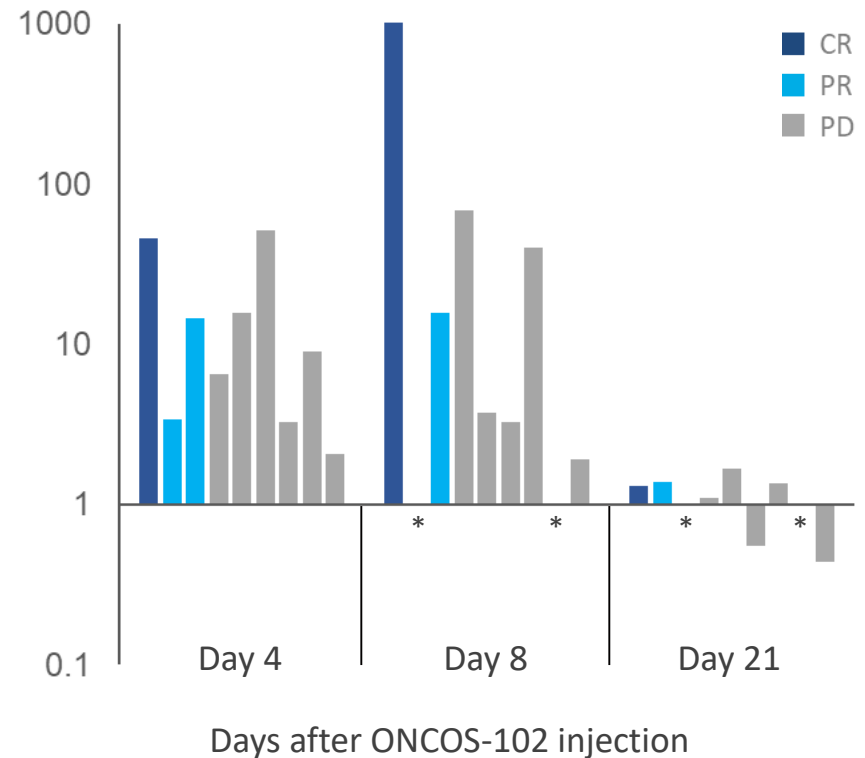
Fold-change CD68+ macrophages vs. survival Intra-tumoral, ONCOS-102 monotherapy

$r = 0.74$ $p = 0.006$

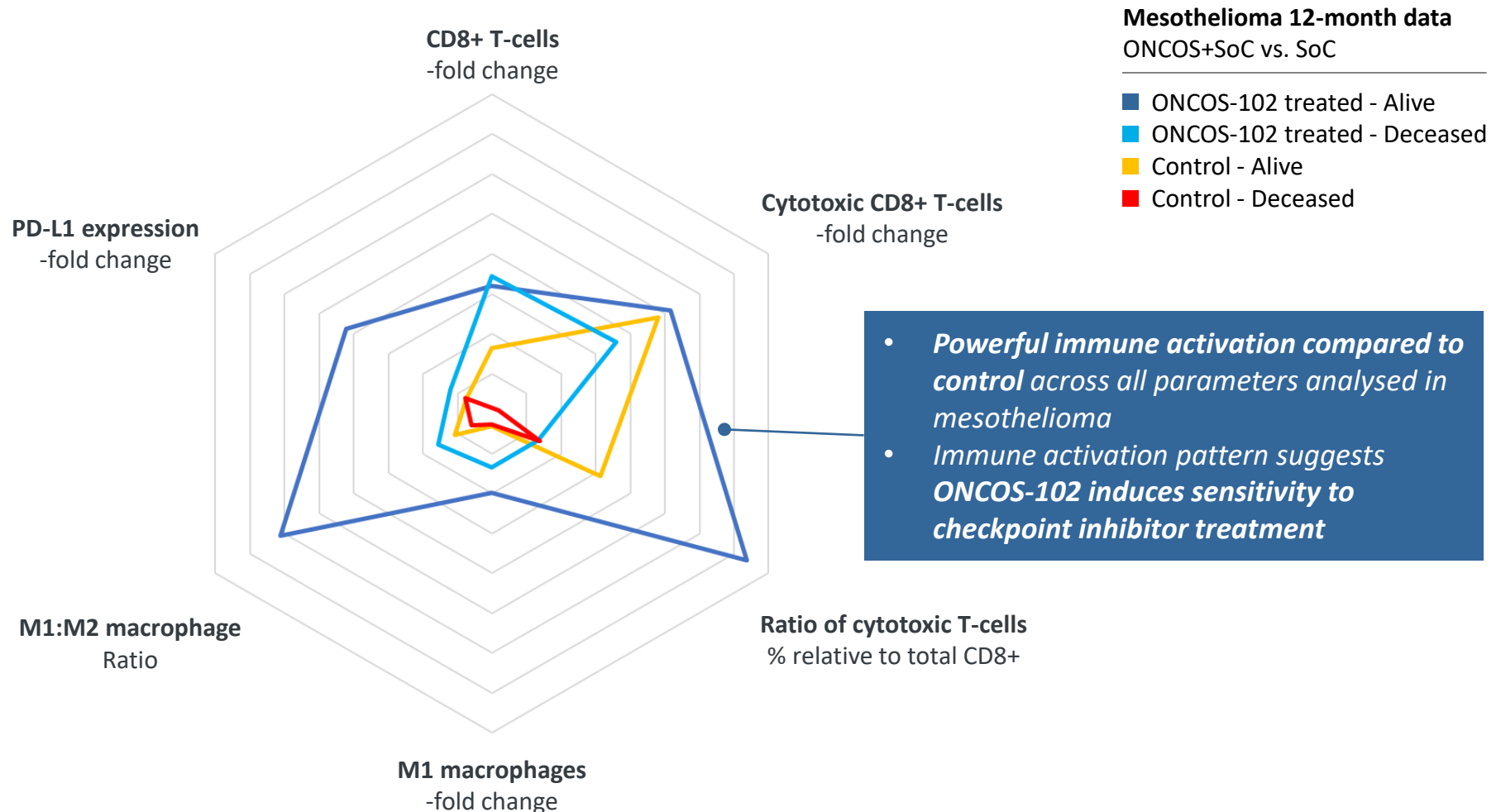


Systemic IL6 expression

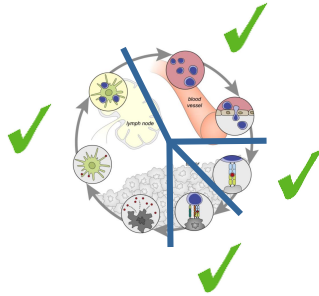
Fold change from baseline, PD1 refractory melanoma



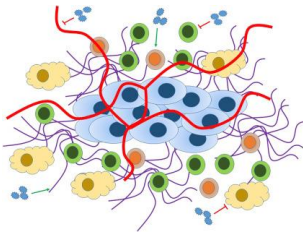
THIS BROAD AND POWERFUL IMMUNE ACTIVATION IS LINKED TO CLINICAL BENEFIT FOR THE PATIENT



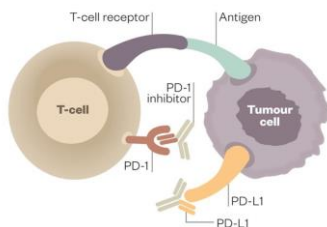
ONCOS-102 IMMUNE ACTIVATION - CONCLUSIONS



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










Multifaceted modulation of the tumor micro-environment induced by ONCOS-102 is linked to clinical benefit in patients with different tumor types



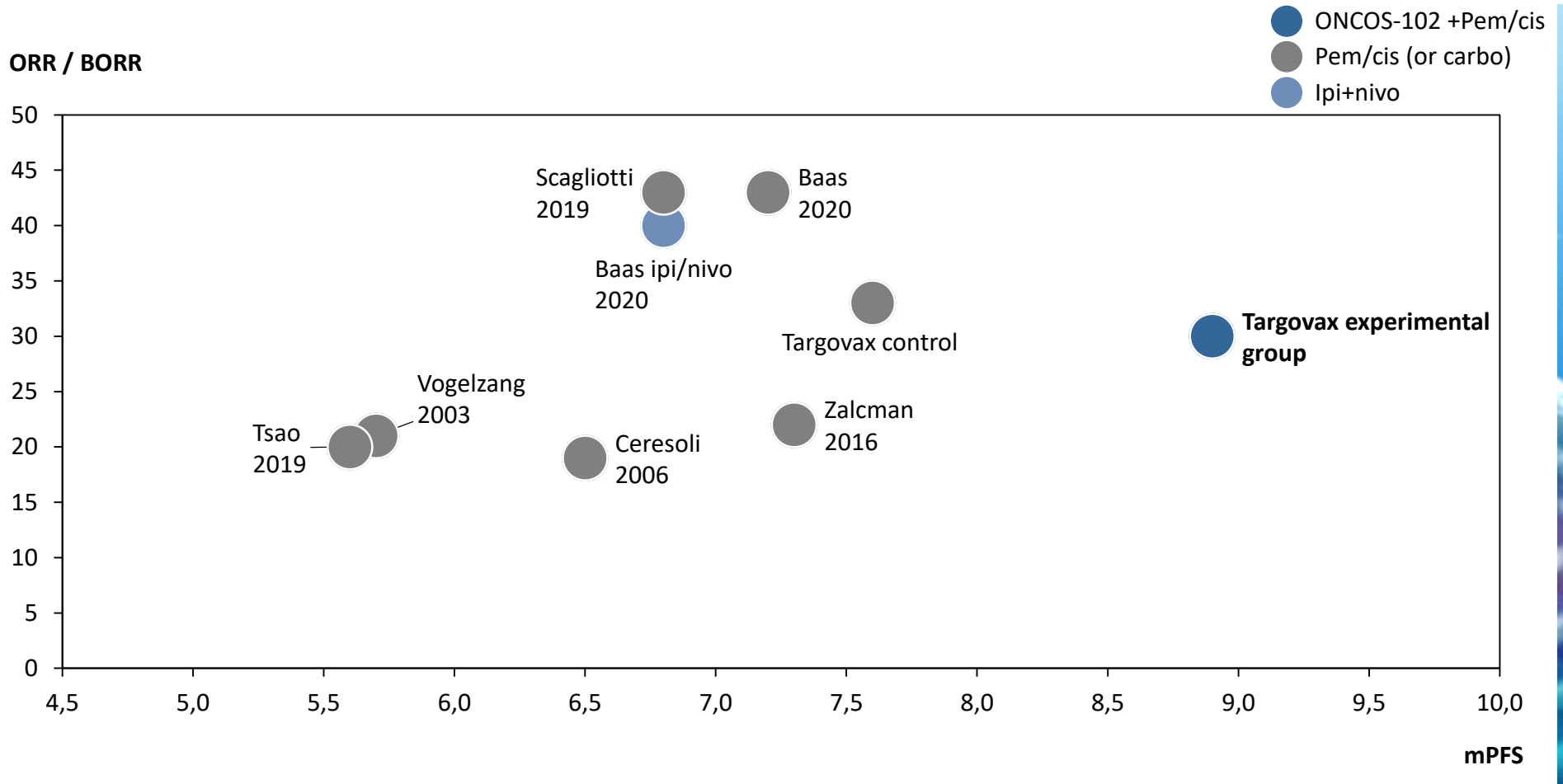
ONCOS-102 induced immune activation provides **broad and powerful priming to sensitize patients** to respond to subsequent treatment with **checkpoint inhibitors**

DEVELOPMENT PROGRAM FOCUSED ON STRATEGIC COLLABORATIONS AND COMBINATIONS

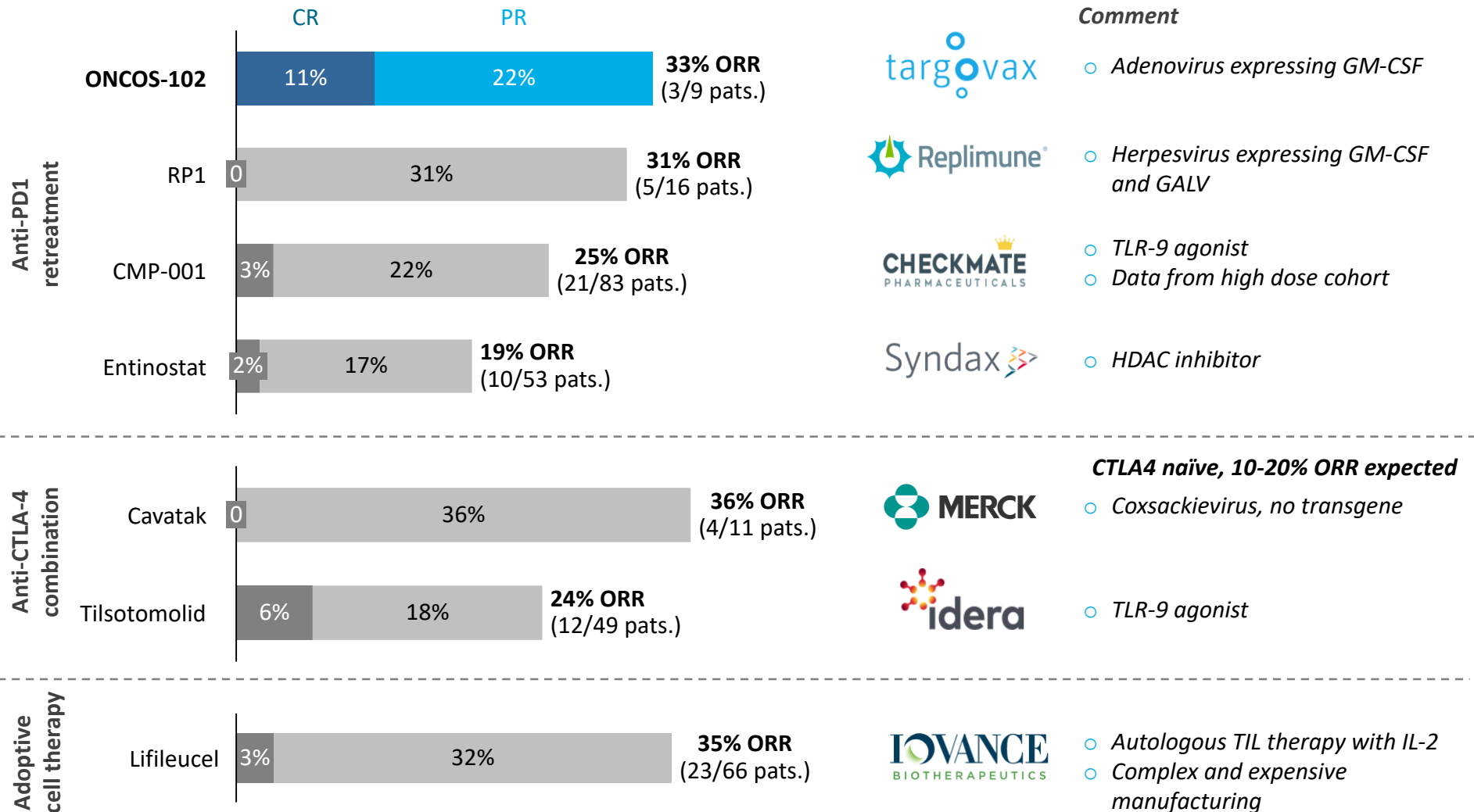
Product candidate	Preclinical	Phase I	Phase II	Collaborator	Next expected event
ONCOS-102	Mesothelioma Combination w/ pemetrexed/cisplatin			 MERCK	2H20 Survival data 2021 New trial with Keytruda
	Melanoma Combination w/Keytruda				2H 2020 Part 2 clinical and immune activation data
	Ovarian and colorectal Combination w/Imfinzi			 AstraZeneca  CANCER RESEARCH INSTITUTE	<i>Update by collaborator</i>
	Prostate Combination w/DCvac			 sotio	<i>Update by collaborator</i>
ONCOS-200 series	Next Gen viruses			 leidos	<i>Updates at conferences</i>
Novel mutRAS concepts				 VALO THERAPEUTICS  OBLIQUE THERAPEUTICS	

CLINICAL BENEFIT DEMONSTRATED IN MESOTHELIOMA

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



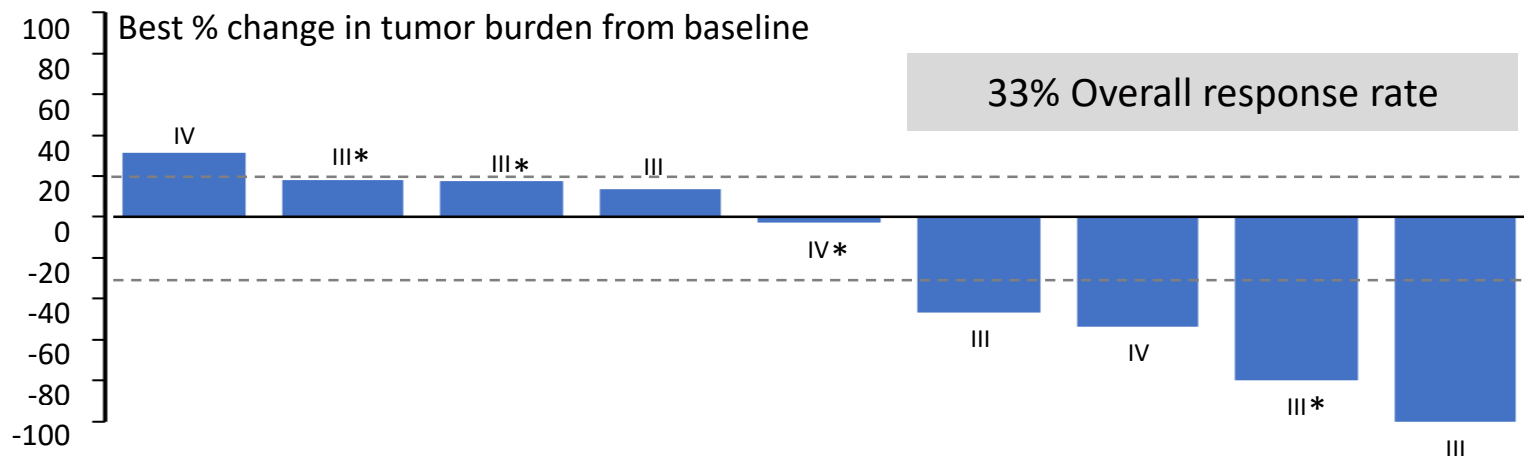
ONCOS-102 HAS PRODUCED EFFICACY DATA COMPETITIVE TO LEADING DRUG CANDIDATES IN PD1 REFRACTORY MELANOMA



ONCOS-102 + KEYTRUDA IN ANTI-PD1 REFRACTORY MELANOMA

PROMISING OUTCOME IN FIRST NINE PATIENTS

Tumor reduction in target lesions



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



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

NEWS FLOW

Rich news flow 2020-21 from ongoing clinical program

Next step in mesothelioma in collaboration with Merck

Pipeline of first-in-class mutant RAS IO concepts and next generation oncolytic viruses