

# Activating the patient's immune system to fight cancer

Oncolytic Virotherapy Summit

Boston - 5 December 2018



targovax

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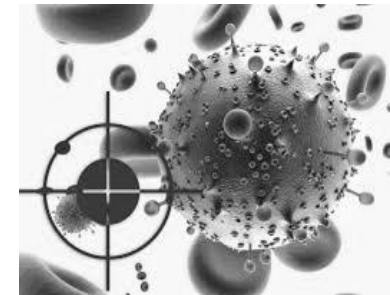
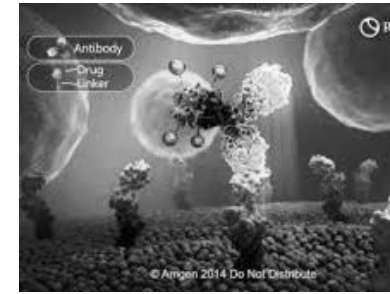
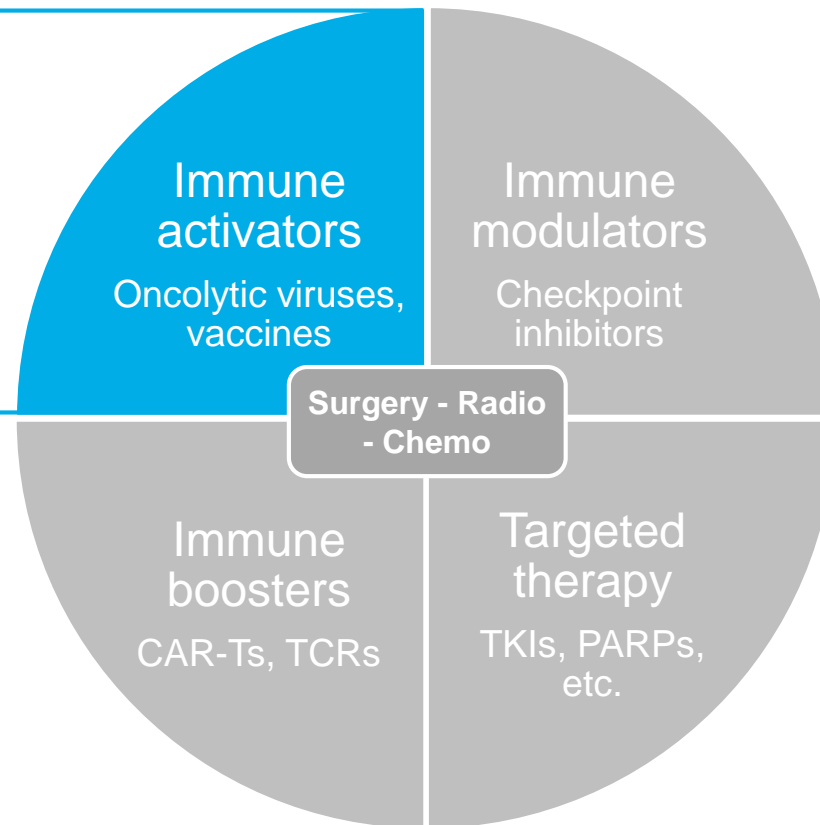
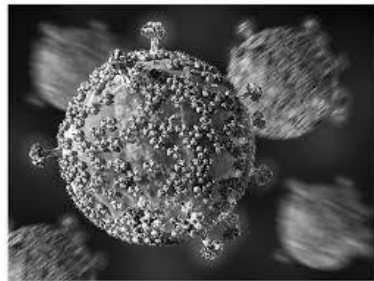
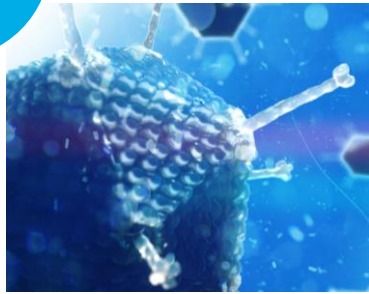
# 1

## Introduction

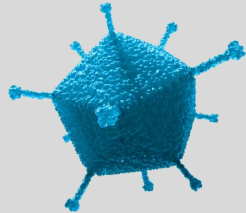
2. Pre-clinical data
3. Phase I single agent data
4. CPI refractory melanoma PD-1 combo data
5. Mesothelioma chemotherapy combo data
6. Summary

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

Targovax focus



# Targovax has two programs in clinical development, with an **ONCOLYTIC VIRUS LEAD PRODUCT CANDIDATE**



**ONCOS**  
Oncolytic virus

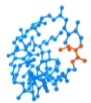
## Lead product candidate

- Genetically **armed adenovirus**
- Turns cold **tumors hot**
- Induces **tumor specific T-cells**
- Single agent **phase I completed**
- **4 ongoing combination trials**

*Activates the  
immune system*

*Triggers patient-  
specific responses*

*No need for  
individualization*

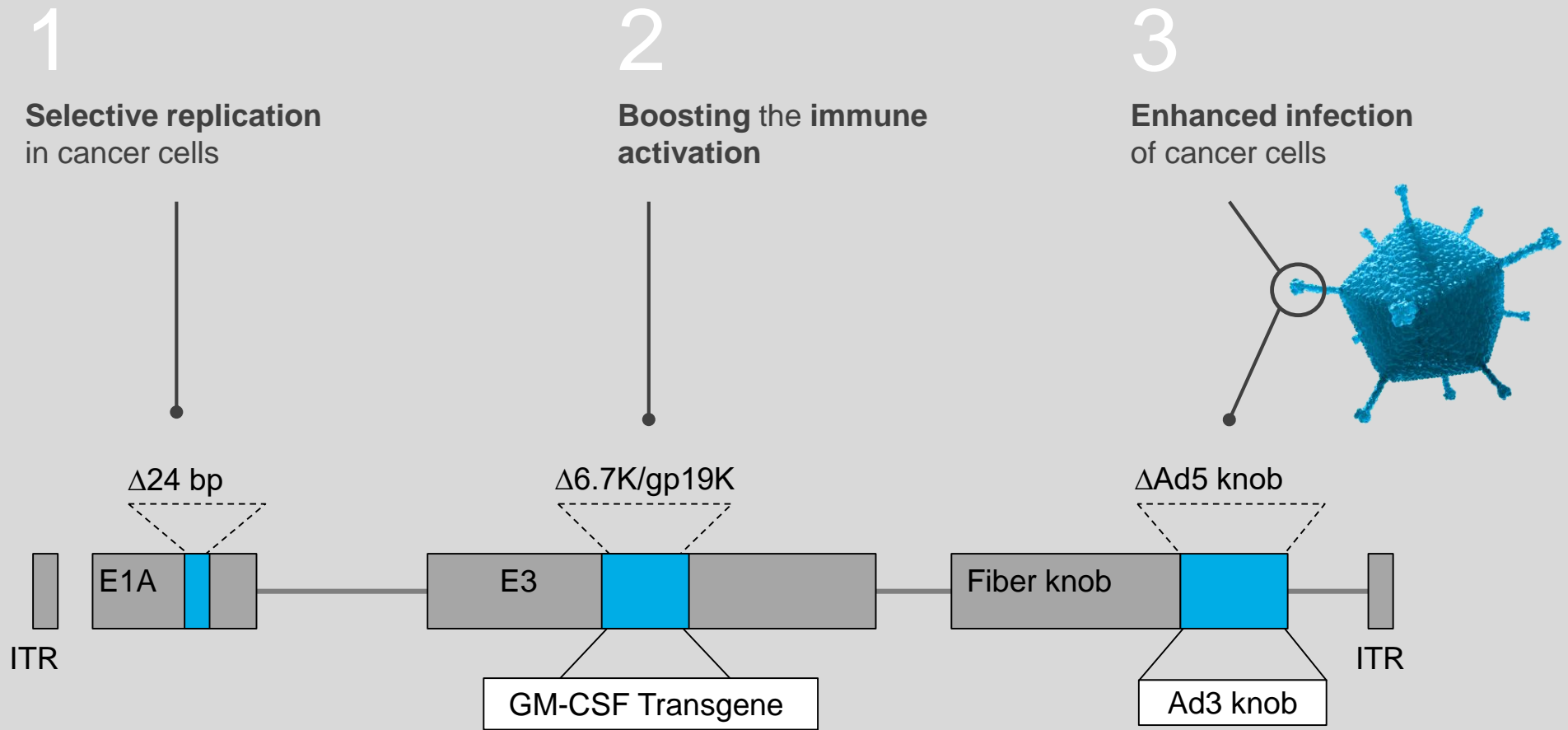


**TG**  
Neoantigen  
vaccine

## Pipeline product

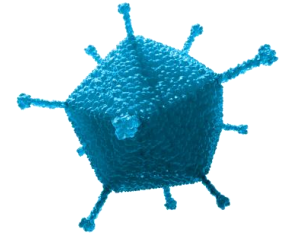
- **Shared neoantigen**, therapeutic peptide vaccine
- Triggers the **T-cell response** to oncogenic **RAS driver mutations**
- 32 patient **phase I/II trial completed**

# ONCOS-102 is a oncolytic adenovirus serotype 5 armed with a GM-CSF transgene





# BENEFITS OF ADENOVIRUS SEROTYPE 5 BACKBONE



**Highly immunogenic**, Toll like receptor 9 (TLR9) agonist



**Well-characterized**, well-tolerated and few safety concerns



**Double stranded DNA**, possibility for transgenes, non-enveloped



**Pre-existing immunity**, reduced issue of immuno-dominance

# PRE-EXISTING IMMUNITY STRENGTHENS

the *in situ* vaccination anti-tumor immune response

## Molecular Therapy



Volume 26, Issue 4, 4 April 2018, Pages 1008-1019

Original Article

### Pre-existing Immunity to Oncolytic Virus Potentiates Its Immunotherapeutic Efficacy

Jacob M. Ricca<sup>1, 2</sup>, Anton Oseledchik<sup>4</sup>, Tyler Walther<sup>1, 2</sup>, Cailian Liu<sup>1, 2</sup>, Levi Mangarin<sup>1, 2, 3</sup>, Taha Merghoub<sup>1, 2, 3</sup>, Jedd D. Wolchok<sup>1, 2, 3, 5</sup>, Dmitriy Zamarin<sup>1, 2, 3, 5</sup>  

*“...pre-existing immunity to NDV may increase its therapeutic efficacy through potentiation of systemic anti-tumor immunity, which provides clinical rationale for repeated therapeutic dosing and prompts investigation of such effects with other OV’s”*

Dmitry Zamarin et al. 2018



# 2

## Pre-clinical data

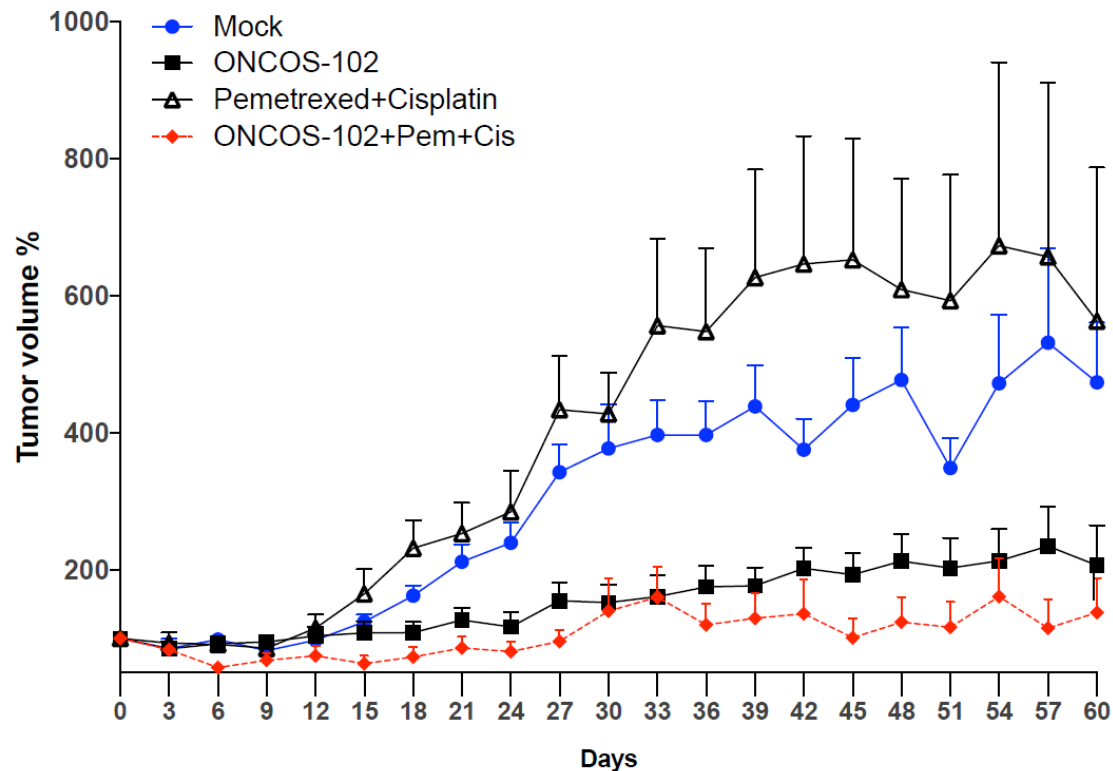
3. Phase I single agent data
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# ONCOS-102 SYNERGY WITH CHEMOTHERAPY

in mesothelioma mouse model

## *In vivo* anticancer effect of ONCOS-102 and chemotherapy

% change in tumor volume



### *Effects observed at Day 60:*

**ONCOS-102 vs. mock**

*56% tumor volume reduction*

**ONCOS-102 vs. pem/cis**

*63% tumor volume reduction*

**ONCOS-102+pem/cis vs. pem/cis**

*75% tumor volume reduction*

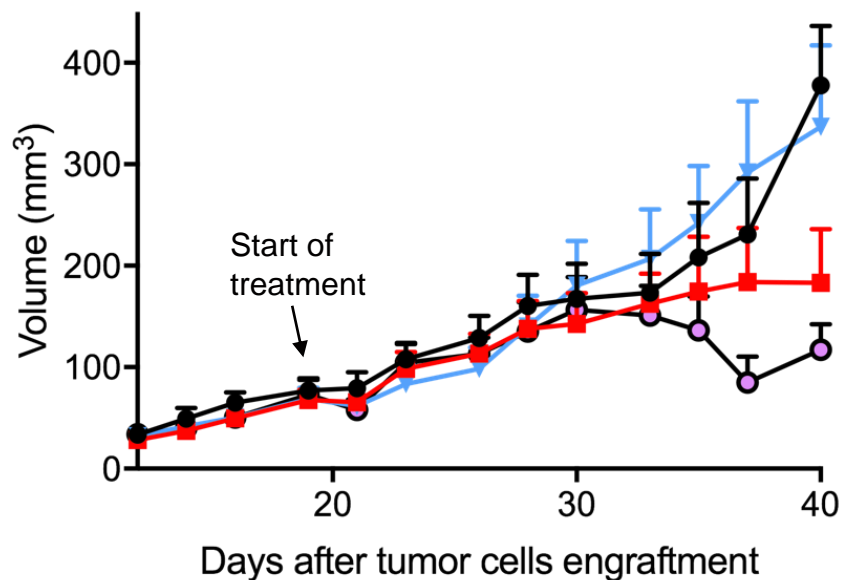
**Combination synergy: ONCOS-102+pem/cis vs. ONCOS-102**

*33% tumor volume reduction*

# ONCOS-102 SYNERGY WITH PD-1 BLOCKADE

in melanoma mouse model<sup>1</sup>

***In vivo* anticancer effect of ONCOS-102 & Keytruda®**  
 % change in tumor volume



**Tumor volume reduction vs. vehicle control**  
 % change by Day 40:

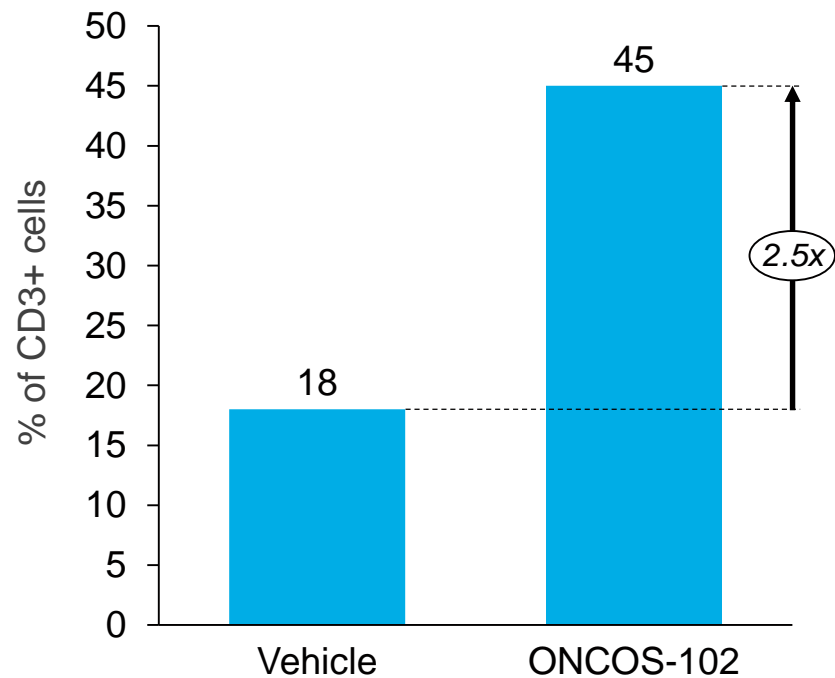
Keytruda® only	No change
ONCOS-102 only	52% reduction p<0.05
ONCOS-102 + Keytruda®	69% reduction p<0.05
Combination synergy effect	35% reduction p<0.05

<sup>1</sup> A2058 cell line xenograft melanoma tumor model, non-responsive to Keytruda® monotherapy treatment

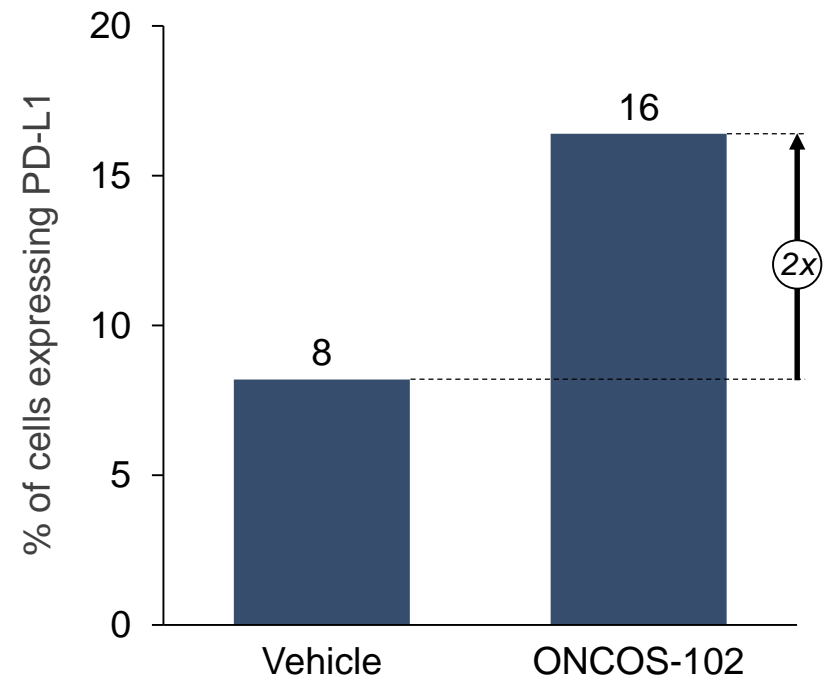
# ONCOS-102 IMMUNE ACTIVATES TUMORS *IN VIVO*

in melanoma mouse model<sup>1</sup>

**CD8+ T-cell tumor infiltration (TILs)**  
% of total CD3+ cell population



**PD-L1 positive tumor cells**  
% of tumor cells



<sup>1</sup> A2058 cell line xenograft melanoma tumor model, non-responsive to Keytruda® monotherapy treatment

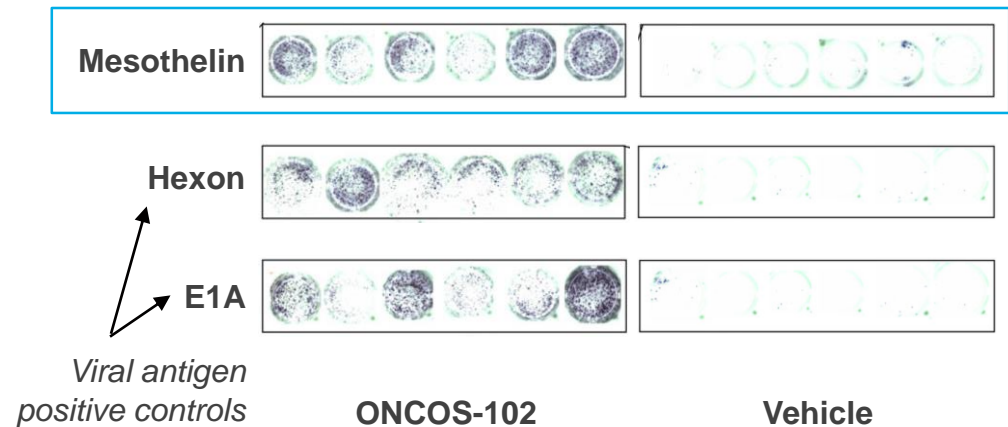
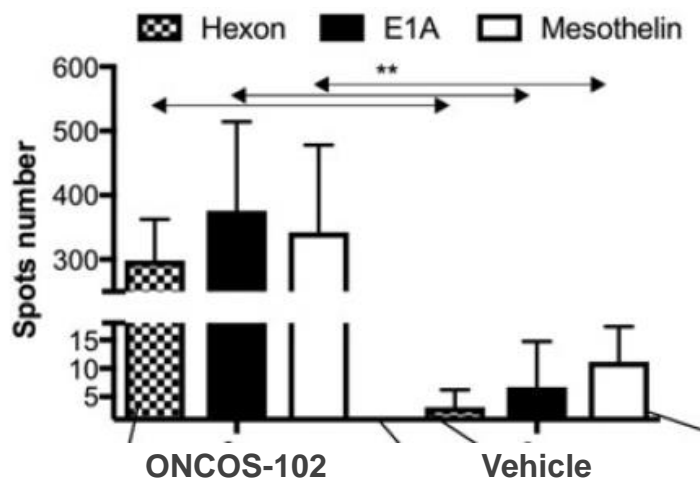
Kuryk et al. Oncoimmunity 2018

# MESOTHELIN-SPECIFIC T-CELL RESPONSE

induced by ONCOS-102 in mesothelioma mouse model

## *In vivo* antigen specific T-cell response

IFN- $\gamma$  ELISPOT analysis for tumor antigen activated T-cells



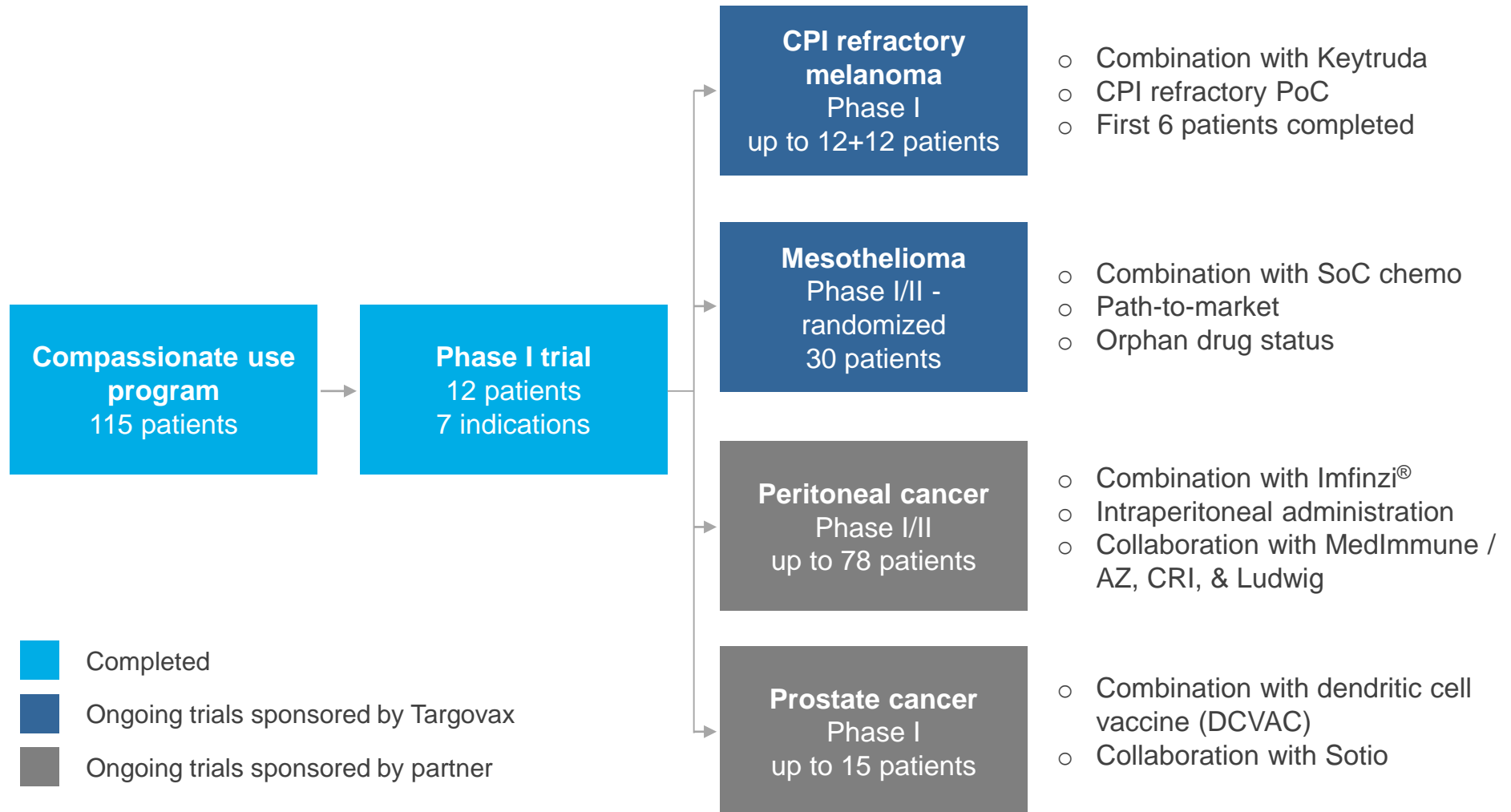
# 3

## Phase I single agent data

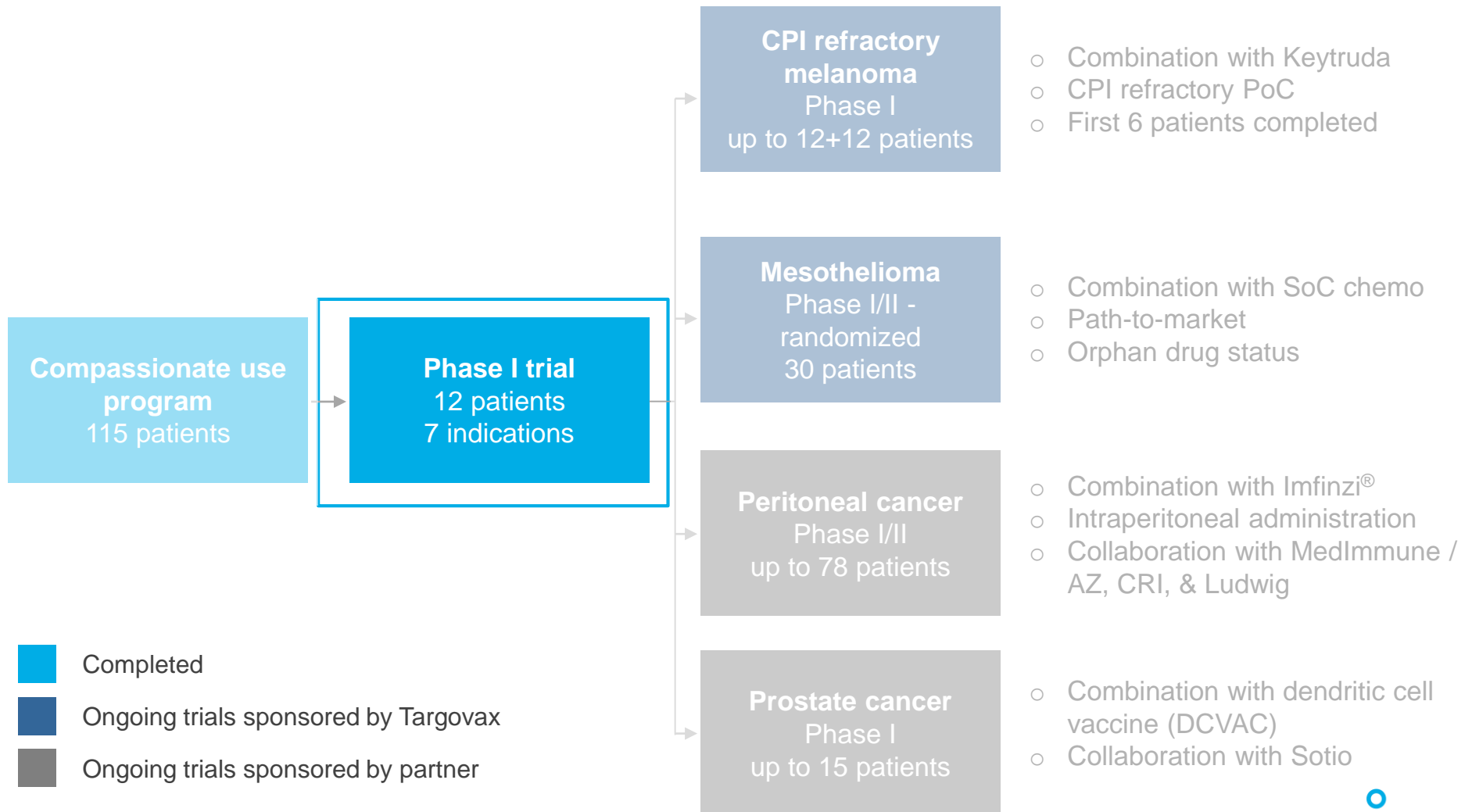
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# ONCOS-102 CLINICAL DEVELOPMENT PROGRAM



# ONCOS-102 PHASE I SINGLE AGENT DATA



# ONCOS-102

Phase I proof of concept

## IMMUNE ACTIVATION DEMONSTRATED

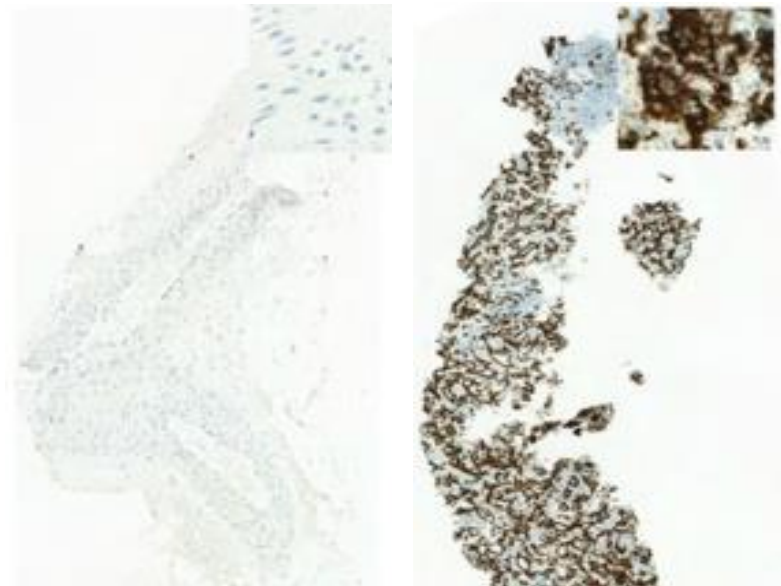
### ONCOS-102 Phase I trial design:

- 12 patients, 7 different solid tumors
- All refractory to multiple lines of therapy
- ONCOS-102 monotherapy
  - 9 injections over 5 months

### Top-line results:

- 100% innate immune activation
- 11/12 patients increase in CD8+ T-cells
- 40% SD, 2 long-term survivors
- Abscopal effect and lasting systemic immune responses observed

Cold tumor turned hot, CD8+ T-cell staining



Pre-treatment  
Baseline

Post-treatment  
Week 8

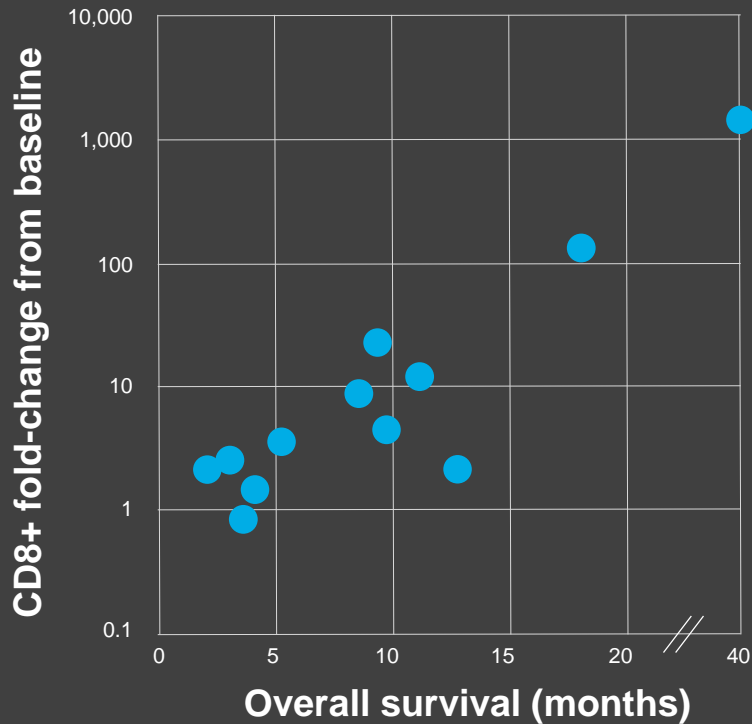
# ONCOS-102

Phase I proof of concept

## CD8+ T-CELL INFILTRATION CORRELATES WITH SURVIVAL

Fold-change CD8+ T-cell count vs. survival

$r = 0.75$   $p = 0.005$



### Case example

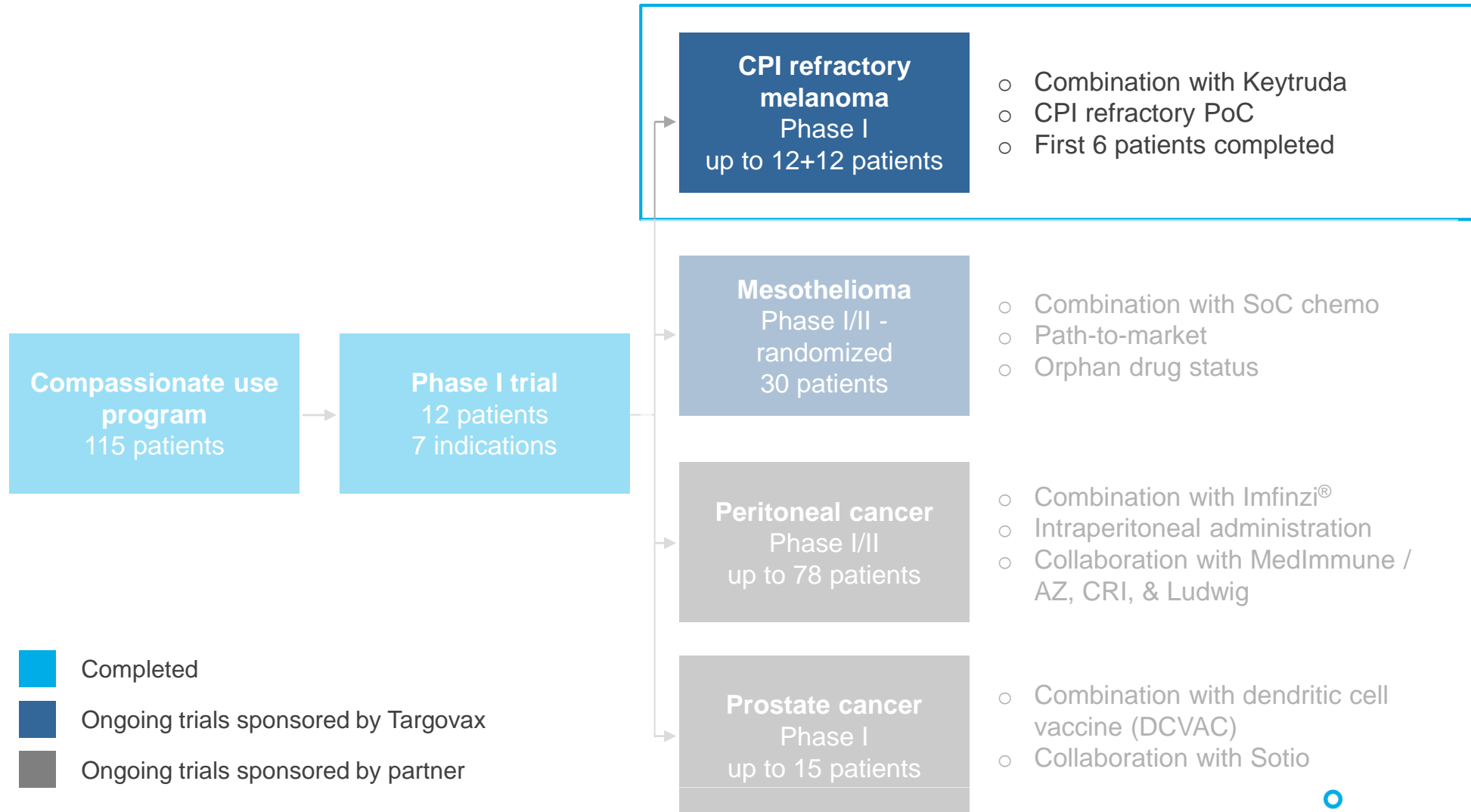
- Ovarian cancer, 38yr old woman
- Failed on 5 types of chemotherapy
- **>1,000-fold increase** in TILs
- **Tumor specific T-cells detected** up to 2 years after treatment
- **Stable disease for 3 years**, survived for 3.5 years

# 4

## CPI refractory melanoma PD-1 combo data

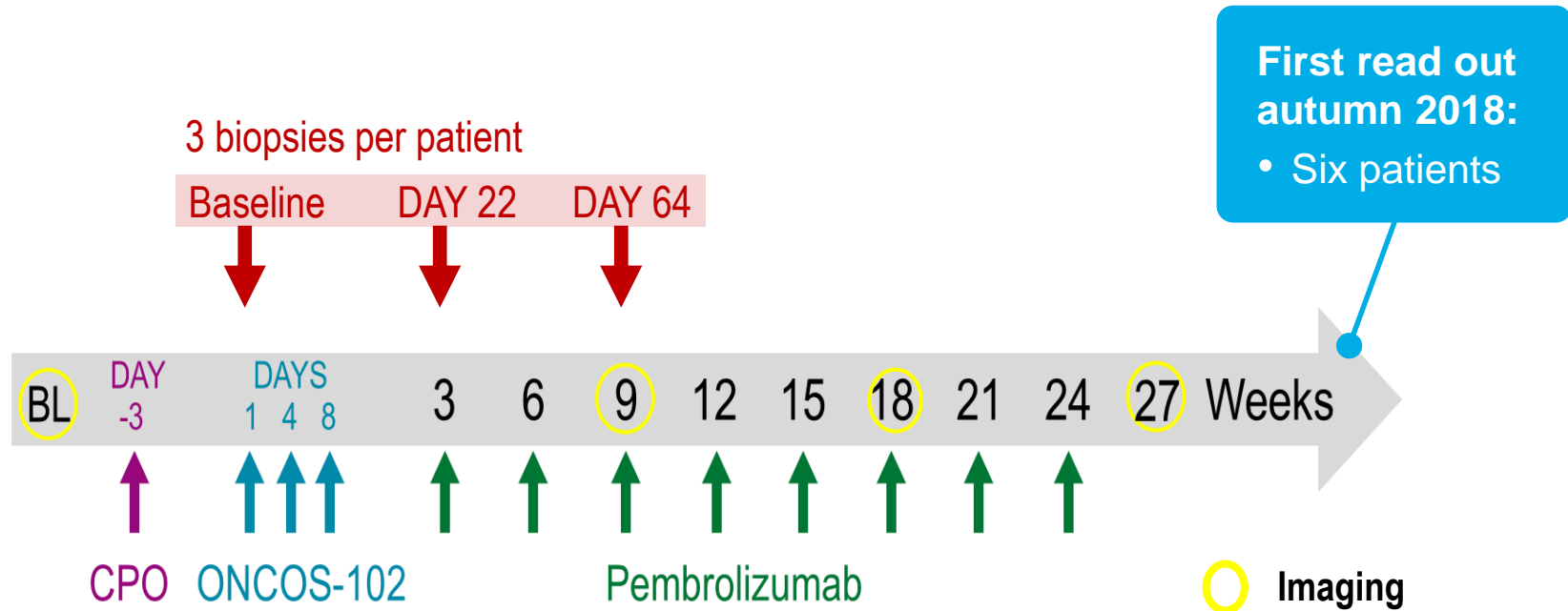
5. Mesothelioma chemotherapy combo data
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# ONCOS-102 MELANOMA EARLY DATA





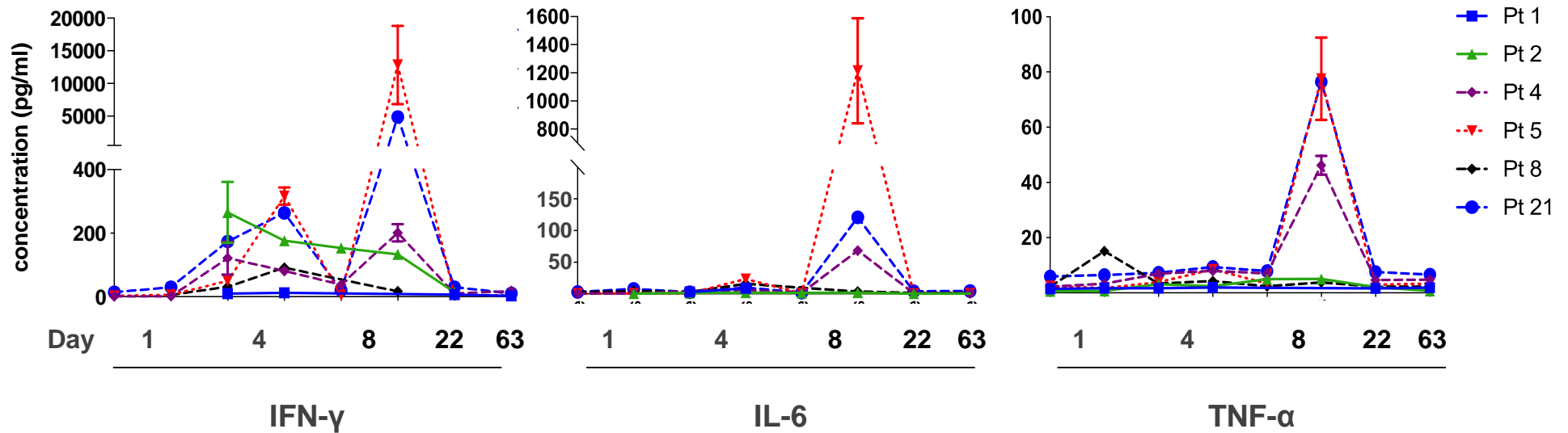
# ONCOS-102 & Keytruda combination MELANOMA PHASE I TRIAL STUDY DESIGN



CPO: Cyclophosphamide

# ONCOS-102 INDUCES INNATE IMMUNE ACTIVATION in CPI refractory advanced melanoma

## ONCOS-102 induction of systemic innate immune response Cytokine expression, concentration in serum

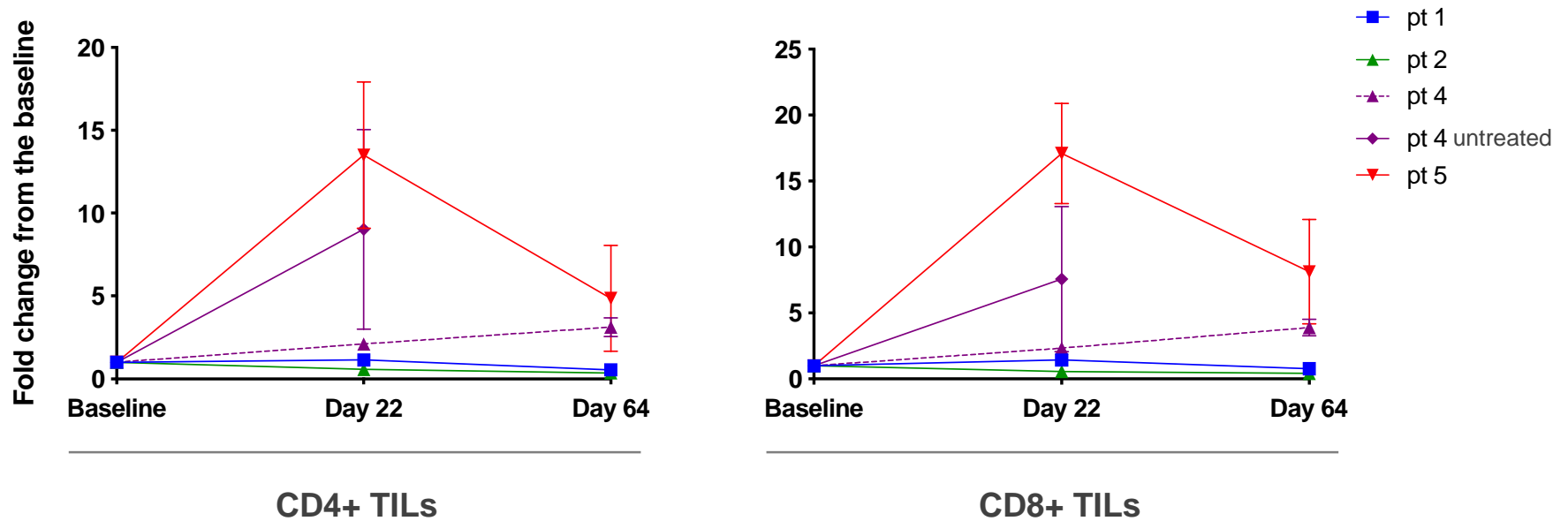


# INCREASED T-CELL TUMOR INFILTRATION

including in un-treated lesion

## Tumor infiltrating lymphocytes (TILs)

Fold change from baseline

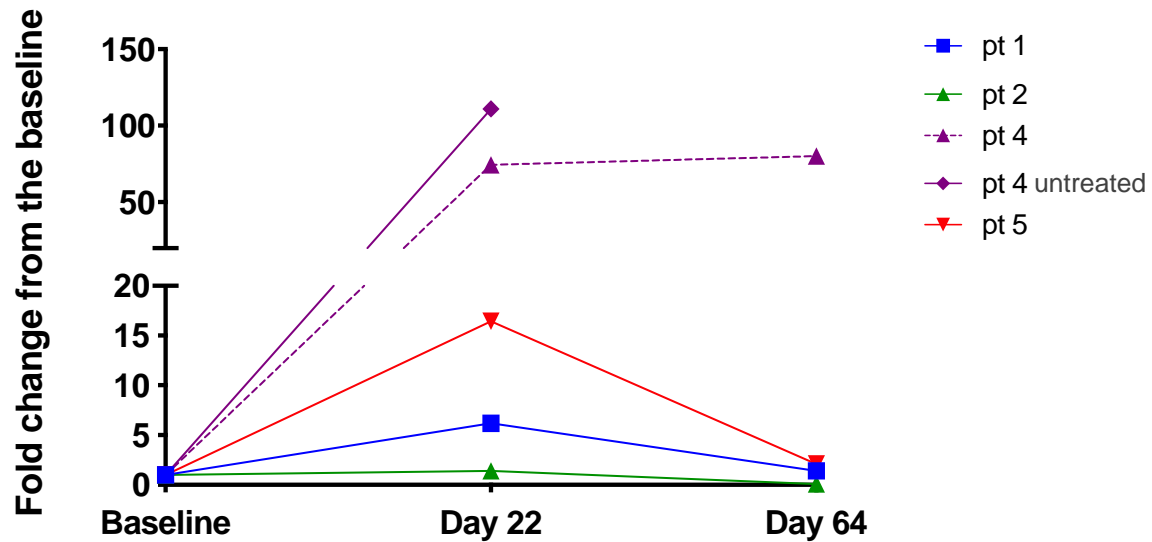


# INCREASED LEVEL OF CYTOTOXIC CD8+ TILs

in patients with strongest immune activation

**Granzyme B expressing CD8+ T-Cells (TILs)**

Fold change from baseline




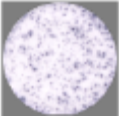

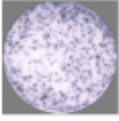


CD8+ GranzB+ TILs

# TUMOR SPECIFIC T-CELLS IN TUMOR BIOPSIES

## Tumor antigen specific T-cell response

IFN- $\gamma$  ELISPOT analysis for tumor antigen activated T-cells

<b>Patient 5</b> <i>Previous Yervoy® &amp; Keytruda</i>	<b>MAGE-A1</b> Week 3		-	<b>Increased infiltration of MAGE-A1 tumor specific T-cells</b> - MAGE-A1 T-cells also detected at baseline
			+	
<b>Patient 4</b> <i>Previous Yervoy, Keytruda &amp; Imlygic®</i>	<b>NY-ESO-1</b> Week 3		-	<b>De novo induction of NY-ESO-1 tumor specific T-cells</b> - Not present at baseline
			+	
	<b>MAGE-A1</b> Week 3		-	<b>De novo induction of MAGE-A1 tumor specific T-cells</b> - Not present at baseline
			+	

# COMPLETE RESPONSE IN PATIENT 5

following ONCOS-102 and Keytruda combination treatment

## Patient 5

*Previous Yervoy & Keytruda*

**Baseline**



*Progression on Keytruda*

**Week 3**



*Visible tumor regression after 3x ONCOS-102 injections*

**Week 9**



*Complete response after 3x ONCOS-102 injections & 2x Keytruda infusions*

## Patient 4

*Previous Yervoy, Keytruda & Imlygic*

**Baseline**

*No clinical benefit with Keytruda monotherapy*

**Week 9**

*SD – Transient tumor regression observed by clinical assessment*

**By week 15**

*Withdrawn due to distant metastasis*



# ONCOS-102 + KEYTRUDA MELANOMA TRIAL

one patient had a complete response by week 9

1

## Safety

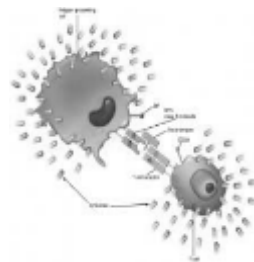
- ✓ **First safety review completed with no concerns**
- ✓ ONCOS-102 and Keytruda combination is well-tolerated



2

## Innate immune activation

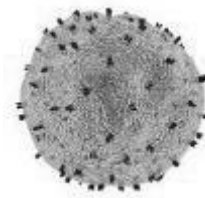
- ✓ **Systemic increase of pro-inflammatory cytokines** (6/6 patients)
- ✓ All patients develop fever



3

## Adaptive immune activation

- ✓ **Increase in tumor T-cell infiltration** (TILs, 3/4 patients)
- ✓ **Tumor-specific T cells** in 2/4 patients
- ✓ **Abscopal immune response** in one patient



4

## Efficacy

- ✓ **Complete response** in 1/6 patients (very rare)
- ✓ **Transient regression** in 3 patients
- ✓ **Associated with level of immune activation**

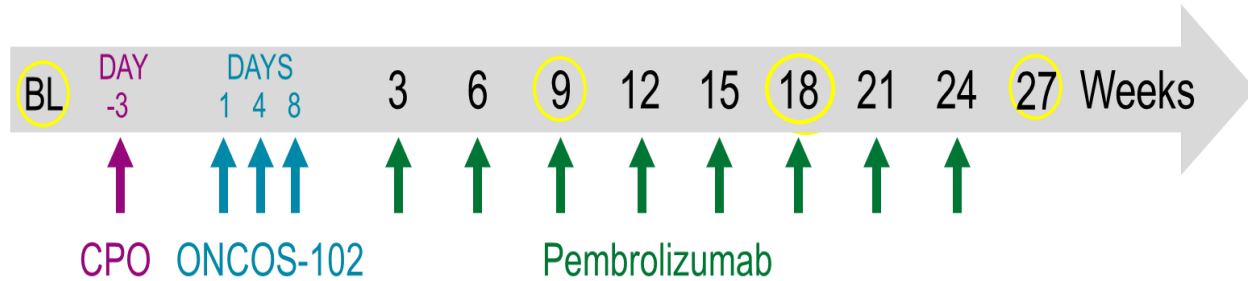


# SECOND DOSE COHORT TO BE INITIATED

up to 12 additional patients who will receive 12 ONCOS-102 injections

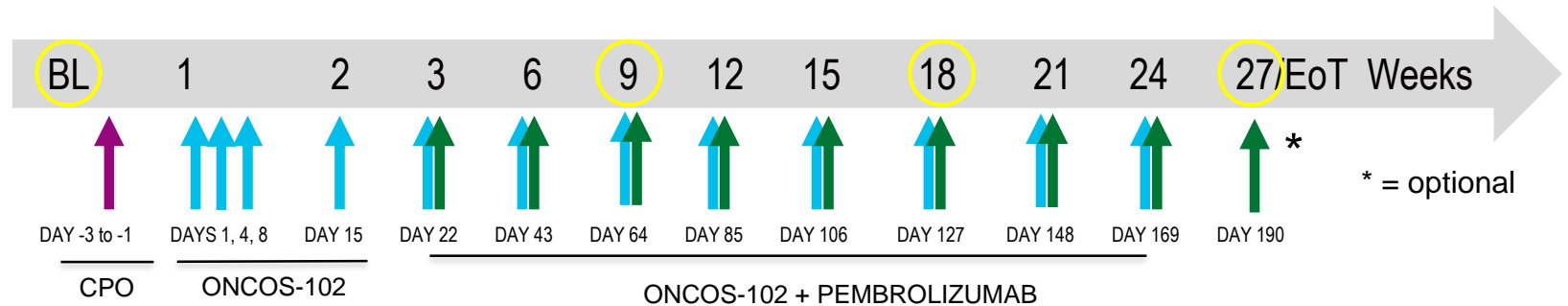
## From:

1<sup>st</sup> dose cohort  
3x ONCOS-102  
injections



## To:

2<sup>nd</sup> dose cohort  
12x ONCOS-102  
injections



○ Imaging

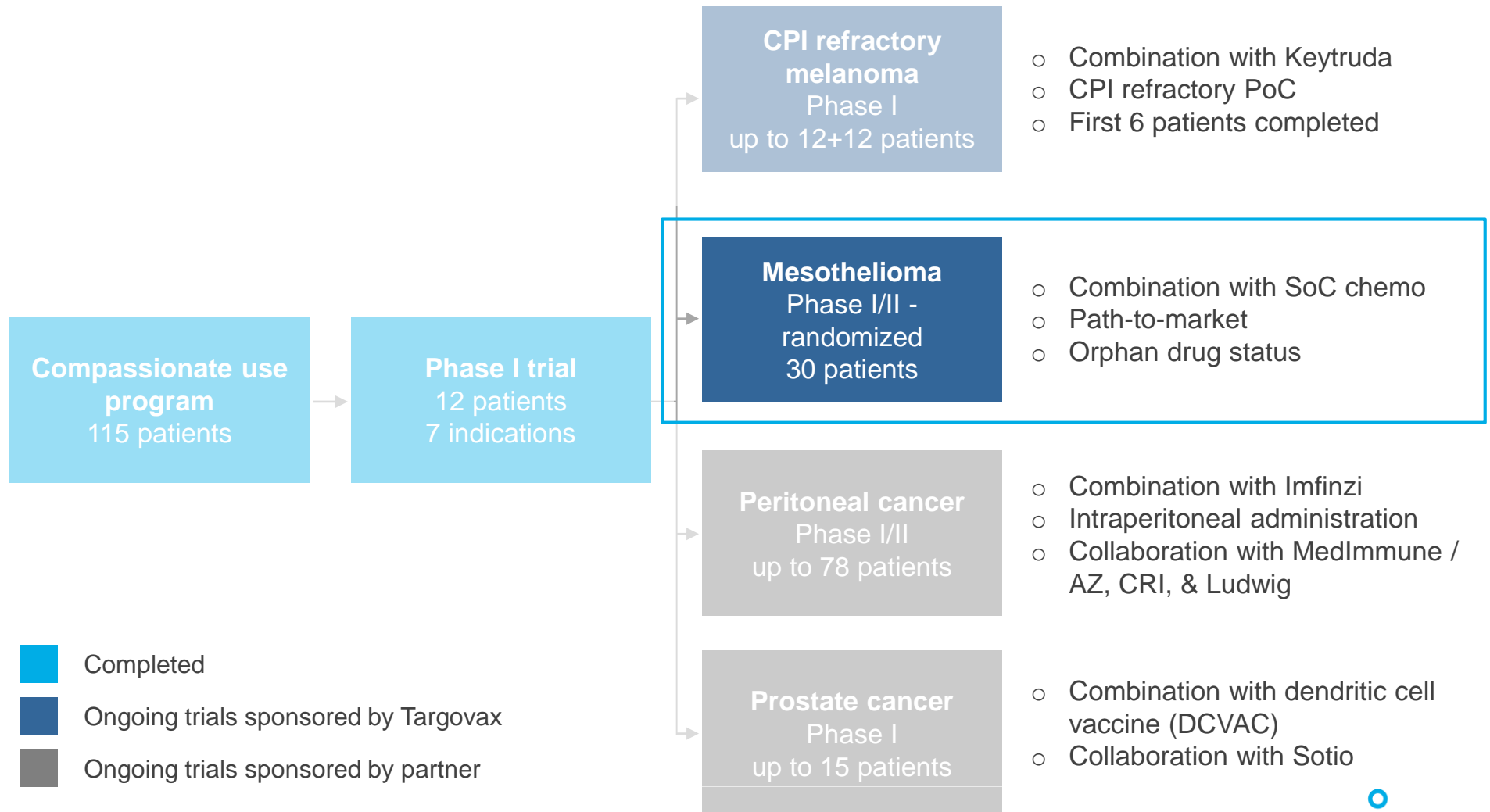
CPO: Cyclophosphamide

# 5

## Mesothelioma chemotherapy combo data

6. Summary

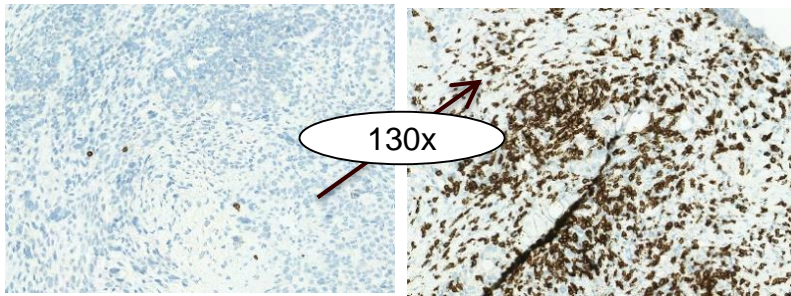
# ONCOS-102 MESOTHELIOMA EARLY DATA



# 2 of 2 mesothelioma patients in Phase I trial showed that ONCOS-102 CAN TURN MESOTHELIOMA HOT

**CD8+ T-cells in tumor**  
Tumor biopsy staining

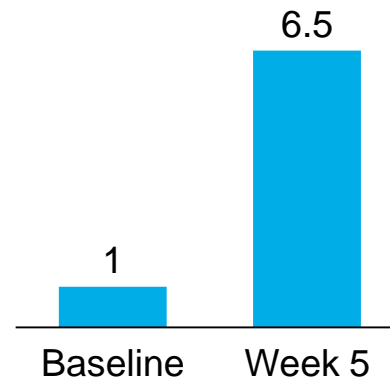
*Mesothelioma – Phase I, patient 14*



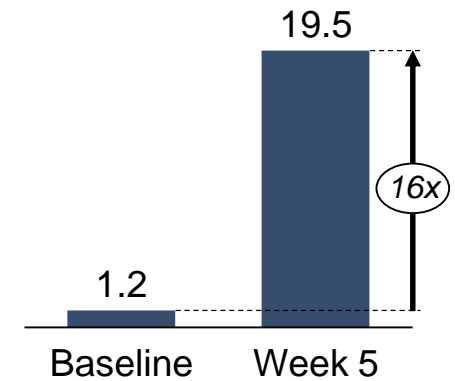
Baseline

Week 5

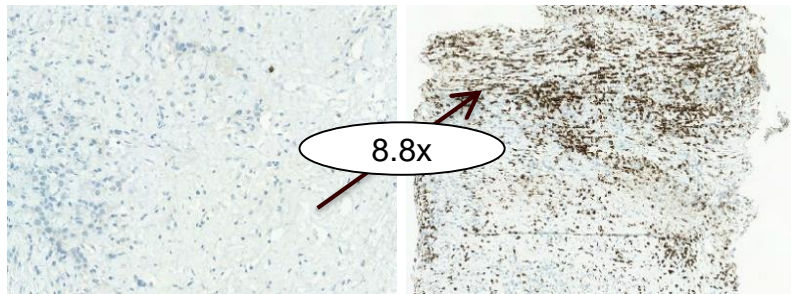
**CD4+ T-cells in tumor**  
Fold change



**PD-L1 positive tumor cells**  
% of total

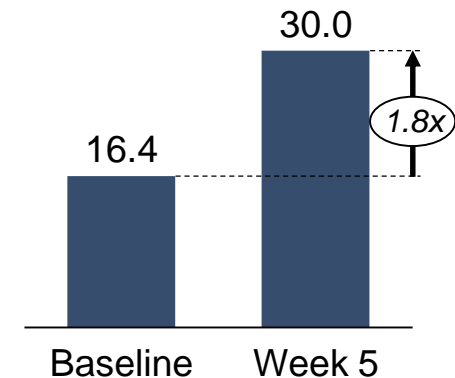
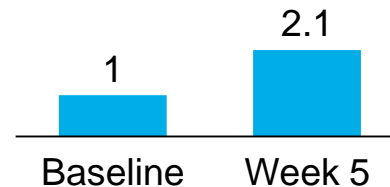


*Mesothelioma – Phase I, patient 9*



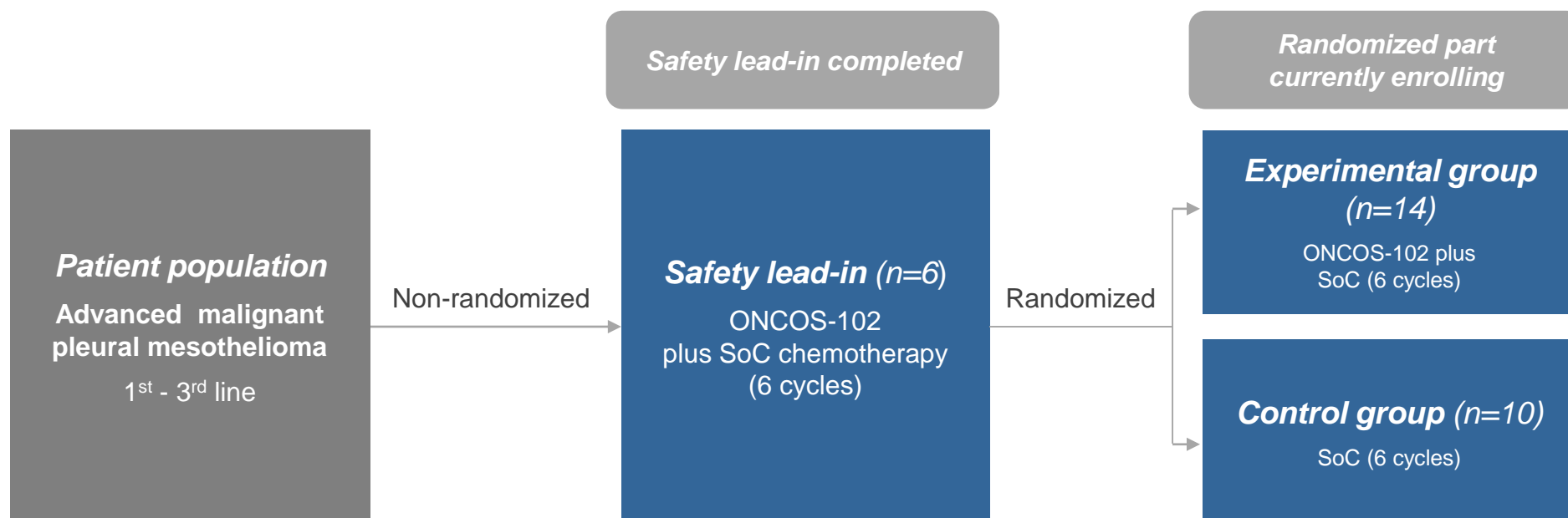
Baseline

Week 5



# ONCOS-102 in malignant pleural mesothelioma

## PHASE I/II STUDY DESIGN IN COMBINATION WITH SoC



# Ongoing ONCOS-102 malignant pleural mesothelioma Phase I/II trial

## SIGNAL OF EFFICACY IN THE FIRST 6 PATIENTS

1

### Safety

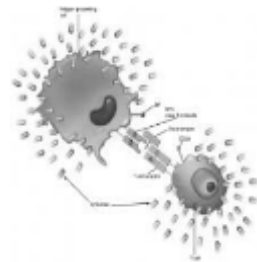
- ✓ ONCOS-102 **well-tolerated** in combination **with chemotherapy**



2

### Innate immune activation

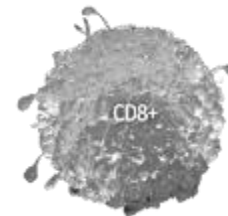
- ✓ **Systemic increase of pro-inflammatory cytokines** in 6/6 patients



3

### Adaptive immune activation

- ✓ Increase in **tumor infiltration of CD4+ and CD8+ T-cells** in 3/4 patients
- ✓ **Tumor-specific T-cells** in 2/6 patients



4

### Efficacy

- ✓ **One partial response (PR)** and two stable disease (SD)
- ✓ **50% disease control rate**



6

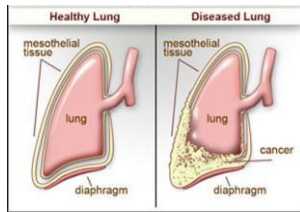
# Summary



# ONCOS CLINICAL DEVELOPMENT STRATEGY

1

**Path-to-market**  
Orphan indication

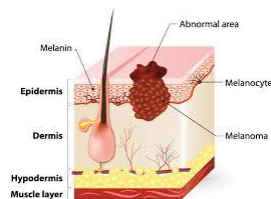


**Target launch indication**

- Mesothelioma
- Orphan drug status
- Combo with SoC chemo

2

**Proof-of-concept**  
Re-activating CPIs



**Reactivating CPI refractory cancers**

- CPI refractory melanoma
- Combo w/PD-1

3

**Proof-of-concept**  
New CPI indication

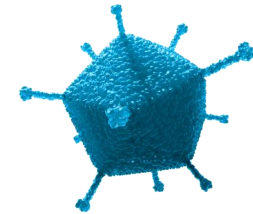


**Indications with no/limited effect of CPIs**

- Ovarian and colorectal cancer with spread to peritoneum
- Combo w/PD-L1

4

**Next generation**  
oncolytic viruses



**Platform expansion with new targets**

- Ongoing pre-clinical testing
- Novel targets and mode-of-action

# WHY ONCOS-102?

1

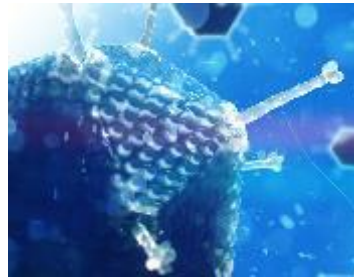
In vivo efficacy



- **Anti-tumor effect**
- **Abscopal effect**
- **Tumor-specific immune responses**
- **Synergy** with both **CPIs and chemo**

2

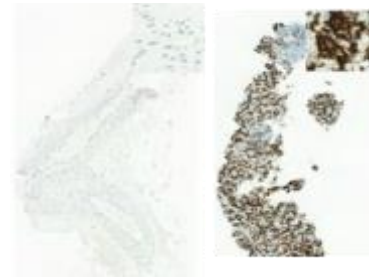
Innate immune activation



- **Strong innate immune activation** in nearly all injected patients
- **Correlation with clinical outcome**

3

Adaptive immune activation



- **Increase in T-cells** systemically and in tumor (TILs)
- **Tumor-specific T-cells** identified in several patients

4

Efficacy



- **Complete response** seen in CPI refractory melanoma patient
- Outcome associated with immune activation
- **Well-tolerated**, >150 patients treated

7

BACKUP

# PIPELINE OVERVIEW AND MILESTONES

Platform	Product candidate	Preclinical	Phase I	Phase II	Phase III	Last event	Next expected event	
ONCOS oncolytic adenovirus	ONCOS-102	Mesothelioma Comb. w/ pemetrexed/cisplatin <sup>1</sup>					Phase Ib safety lead-in cohort, incl. immune activation and ORR data (6 pts)	<b>1H 2020</b> Randomized ORR data 30 pts
		Melanoma Comb. w/KEYTRUDA®					ORR and immune activation (6 pts), 1/6 CR	<b>1H 2019</b> ORR and immune data first cohort
		Peritoneal cancers <sup>2,3</sup> Collab: Ludwig, CRI & AZ Comb. w/IMFINZI®					First dose escalation cohort safety review (4 pts)	<i>Update by collaborator, expected 2019</i>
		Prostate <sup>3</sup> Collab: Sotio Comb. w/DCVAC					First patient dosed	<i>Update by collaborator, expected 2019</i>
	Next-gen ONCOS	3 viruses undisclosed					Virus construct cloning and <i>in vitro</i> validation	<b>2H 2019</b> <i>Pre-clinical data</i>
TG neo- antigen cancer vaccine	TG01	Pancreatic cancer Comb. w/gemcitabine					mOS 33.4 months Demonstrated mutant RAS- specific immune activation	TBD
	TG02	Colorectal cancer Proof-of-mechanism Comb. w/KEYTRUDA®					First safety review, incl. immune activation data (3 pts)	<b>1H 2019</b> Immune activation and mechanistic data (mono)
	TG02	CPI synergy TG + PD-1						<b>2019</b> Pre-clinical data

1 Current standard of care chemotherapy for patients with unresectable malignant pleural mesothelioma

2 Patients with advanced peritoneal disease, who have failed prior standard chemotherapy and have histologically confirmed platinum-resistant or refractory epithelial ovarian or colorectal cancer

3 Trials sponsored by collaborators

■ Ongoing collaborator sponsored trials

# Ongoing ONCOS-102 malignant pleural mesothelioma Phase I/II trial

## CLINICAL RESPONSES IN SAFETY COHORT

