targovax

Clinical development of ONCOS-102 oncolytic virus as combination therapy for solid tumors

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The Immuno-Oncology revolution

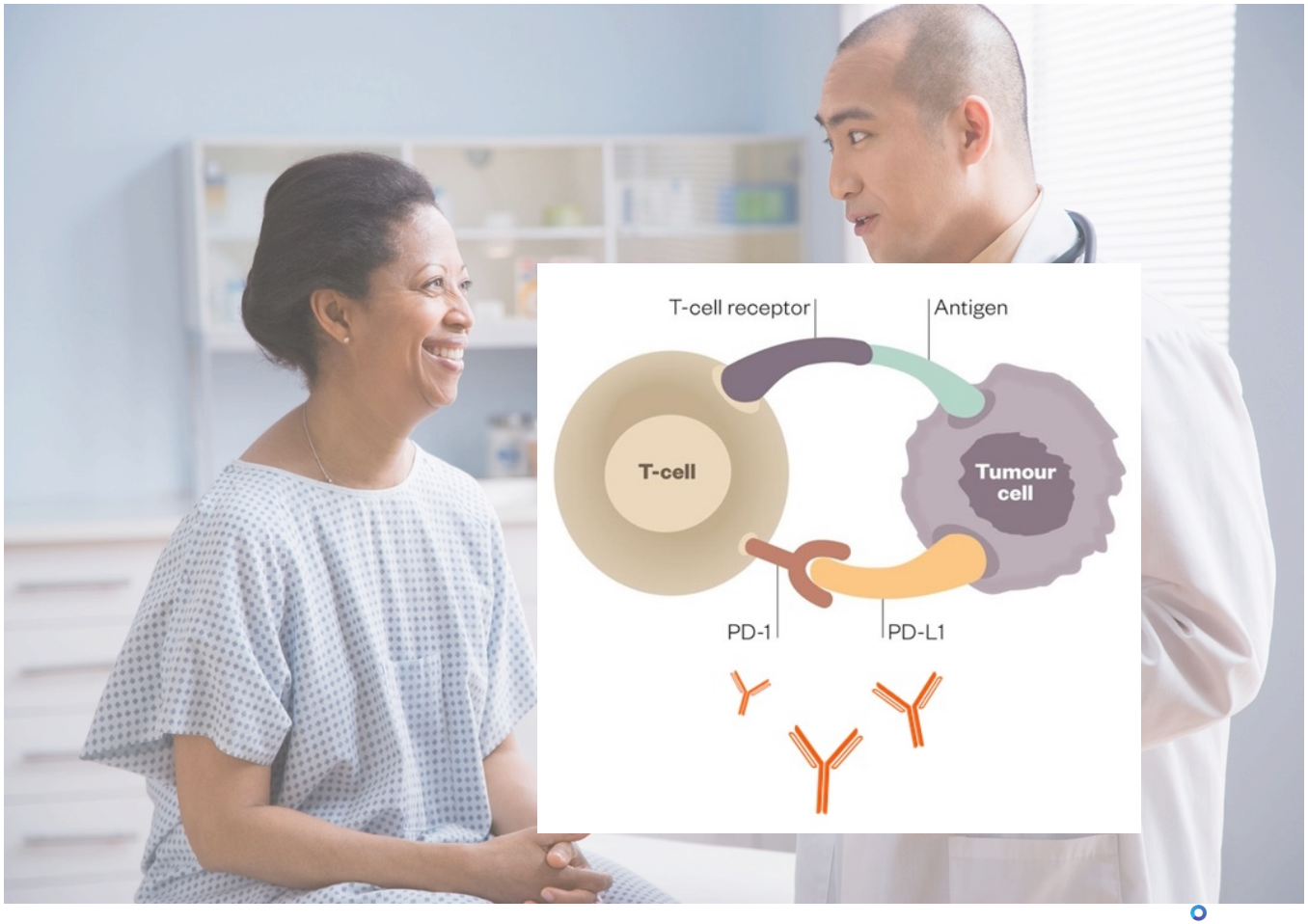
>500,000 patients treated per year

>4,000 ongoing clinical trials

>40% of US cancer patients eligible

First generation Immuno-Oncology: CPIs

- **Cornerstone** of current cancer treatment
- **Deep and durable** responses
- **$30b** annual sales globally
- **8 products** approved to date, many more in development



0-40% of treated patients respond

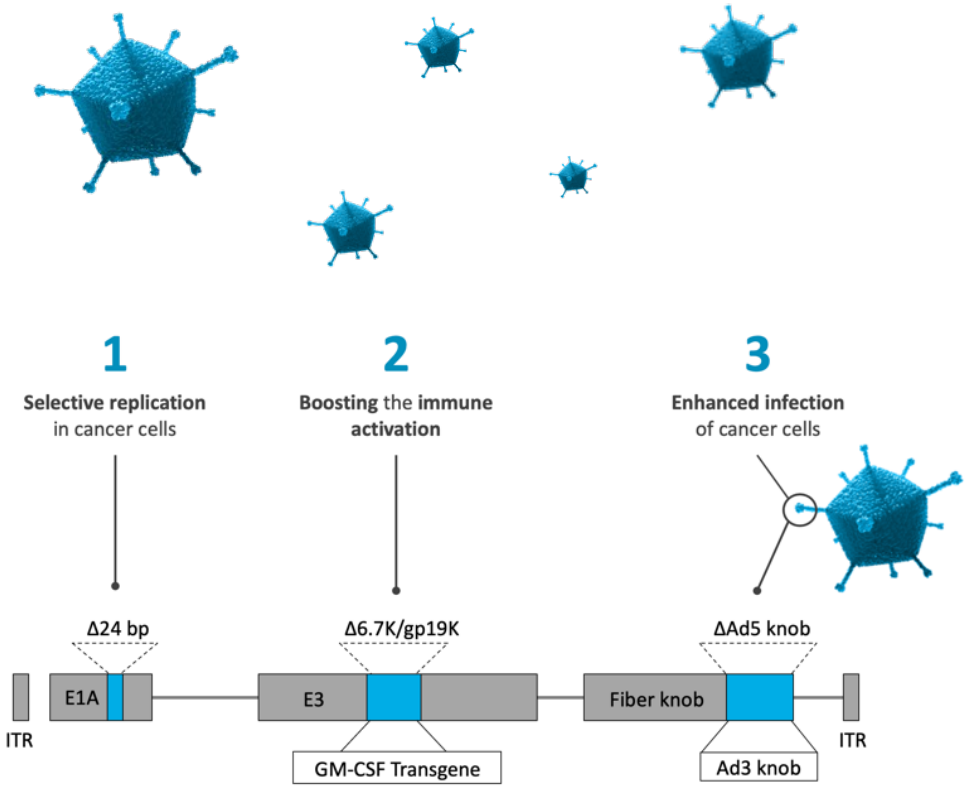
>50% of responding patients relapse

1 PD-1 checkpoint inhibitor monotherapy not sufficient

THE CHALLENGE:

MAKE CHECKPOINT INHIBITORS WORK FOR MORE PATIENTS

ONCOS-102 is an oncolytic immunotherapy based on an adenovirus serotype 5 backbone

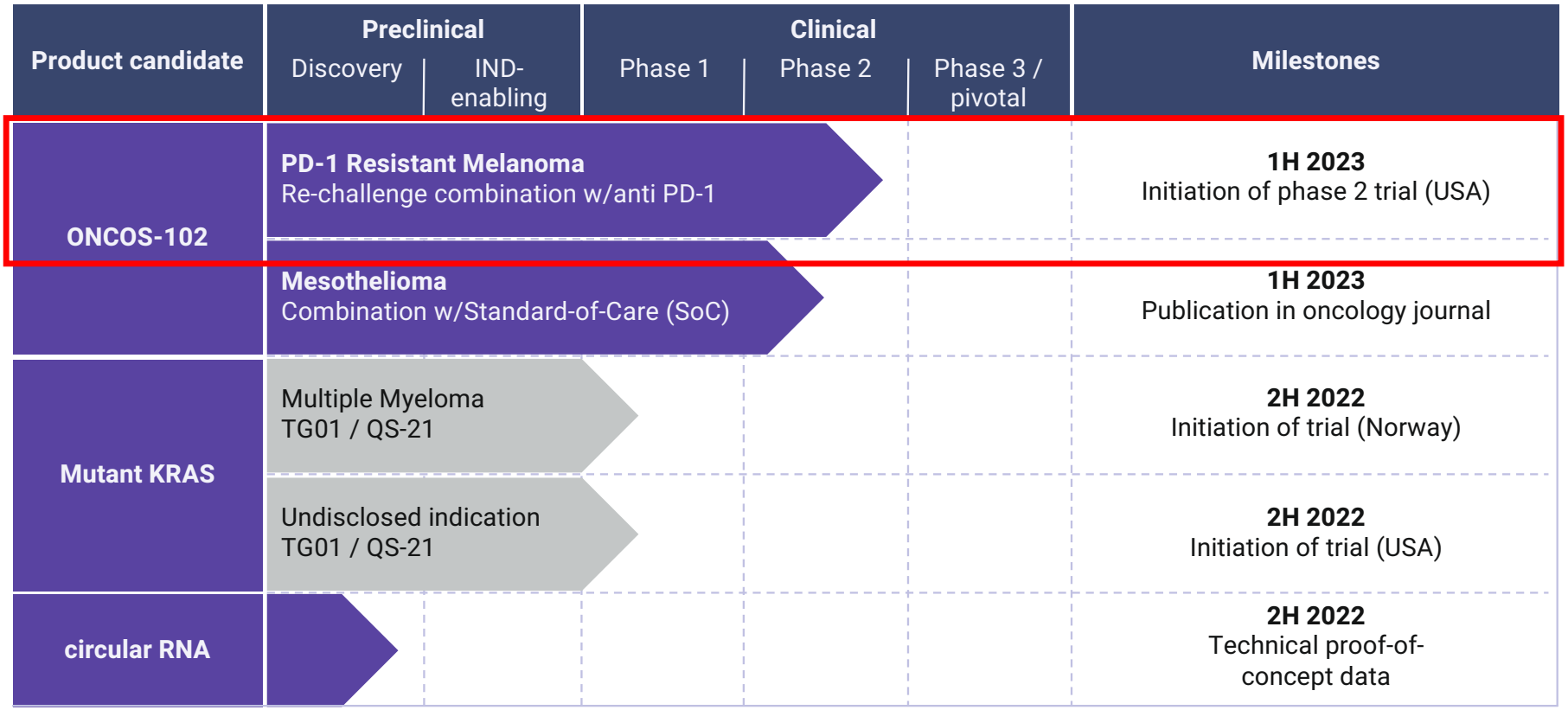


Reverses immuno-suppressive defence mechanisms in the tumor

Primes anti-cancer T-cell responses

Delivers immune stimulatory payloads

Targovax development pipeline



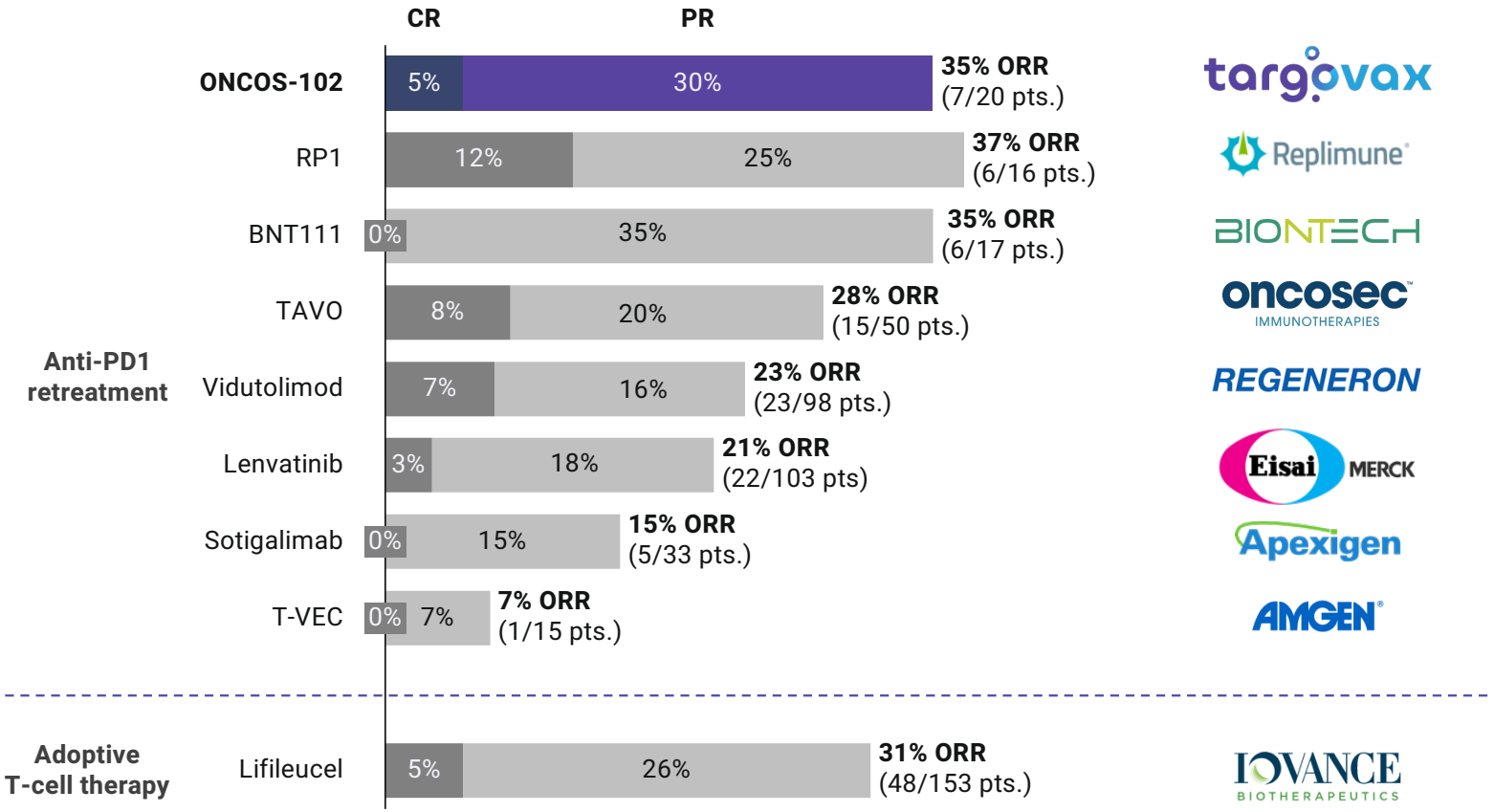
Trials run and financed by collaboration partners

Lead clinical program: ONCOS-102 combination therapy w/CPIs in CPI-resistant advanced melanoma

There is a major and growing unmet medical need in PD-1 resistant melanoma

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***

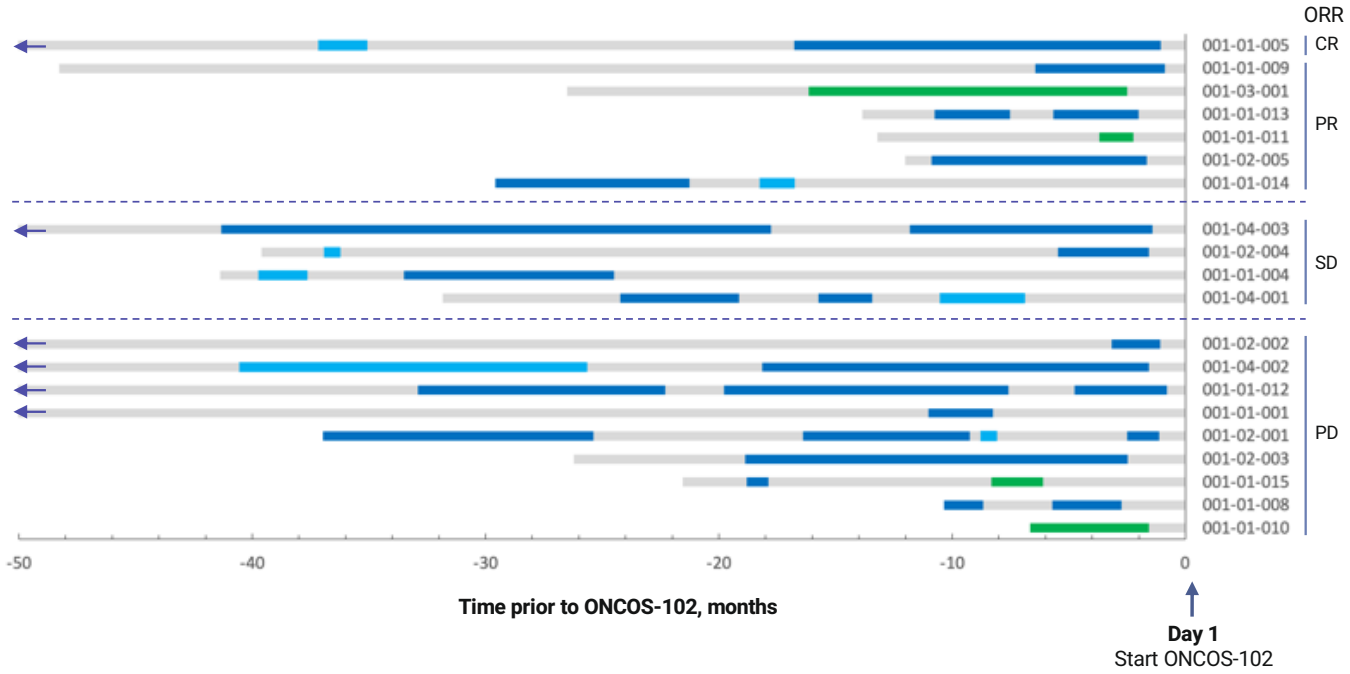
Oncos-102 achieved a highly competitive ORR of 35% in PD-1 resistant melanoma



Targovax assessment, October 2022

Most patients conformed to a strict PD-1 resistance definition, including 6/7 responders

Checkpoint inhibitor treatment prior to enrolling in ONCOS-102 trial

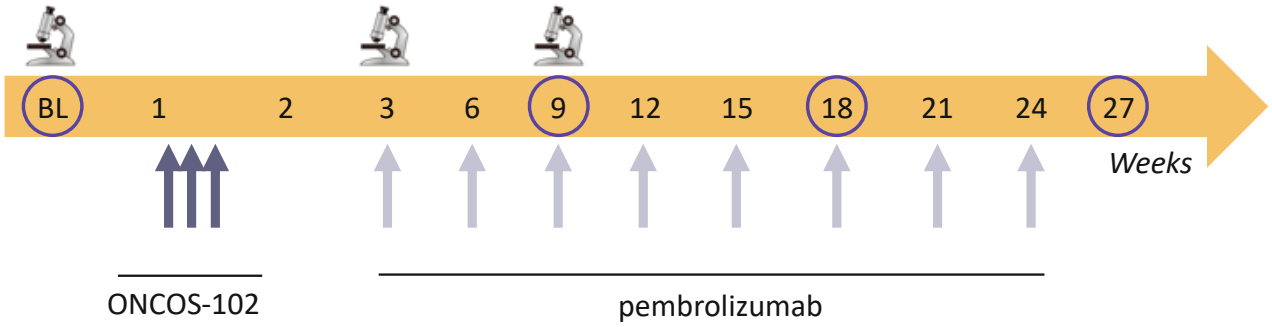


- **All patients had min. 2 cycles of anti-PD1** (nivo or pembro)
- All patients had progression on PD1, **confirmed by CT at baseline**
- **15/20 patients had** last aPD1 treatment < 3 months prior to study (6/7 PR/CR)

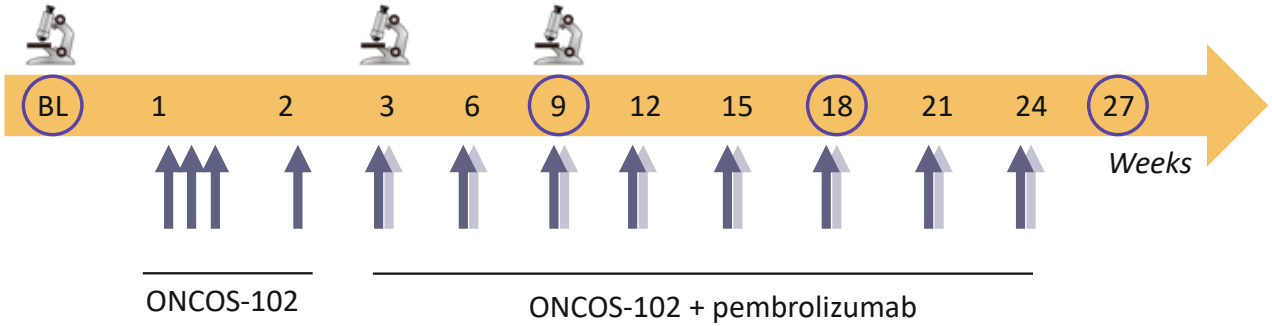
aPD1
aCTLA4
aPD1 + aCTLA4
No or other treatment
← Pts very first anti-cancer treatment > 50 months prior to ONCOS-102
ORR Best Objective Response during study, RECIST 1.1

ONCOS-102 Phase 1B trial in PD-1 resistant advanced melanoma - treatment schedule

Part 1 (n=8):
3x ONCOS-102 injections
Sequential treatment



Part 2 (n=12):
12x ONCOS-102 injections
Combination treatment



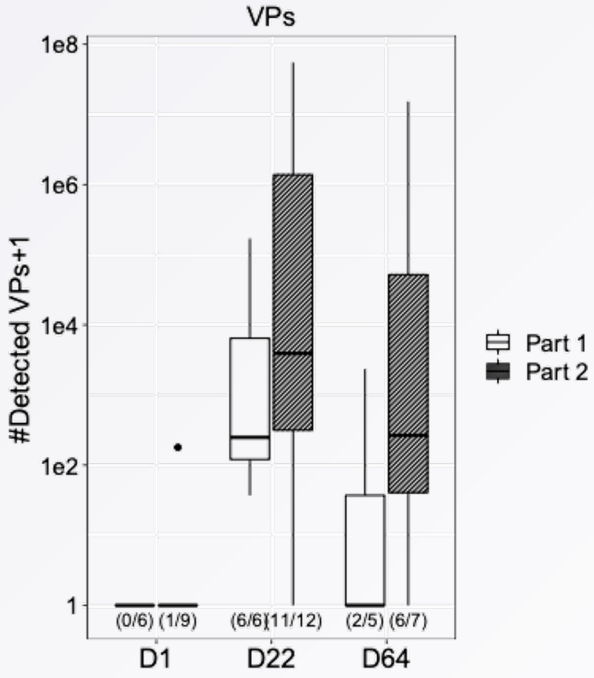
Imaging

Biopsy

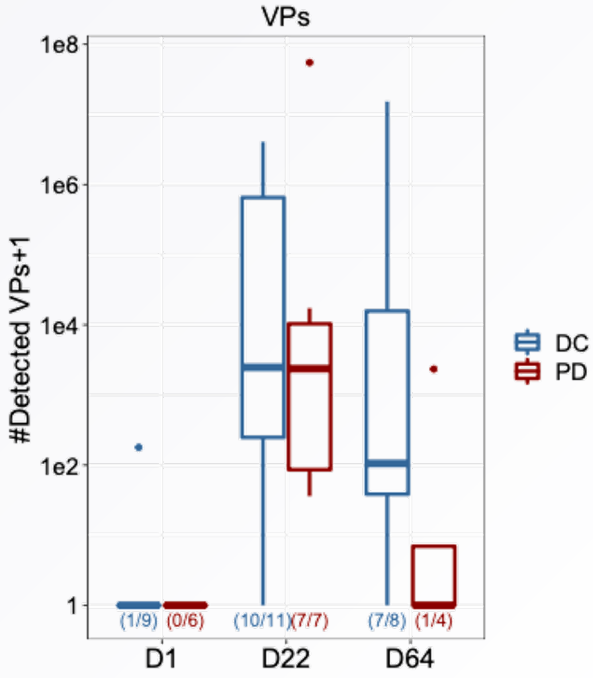
ONCOS-102 is robustly detectable in tumors and remain present in responders at least until week 9

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

Part 1 vs. Part 2 patients

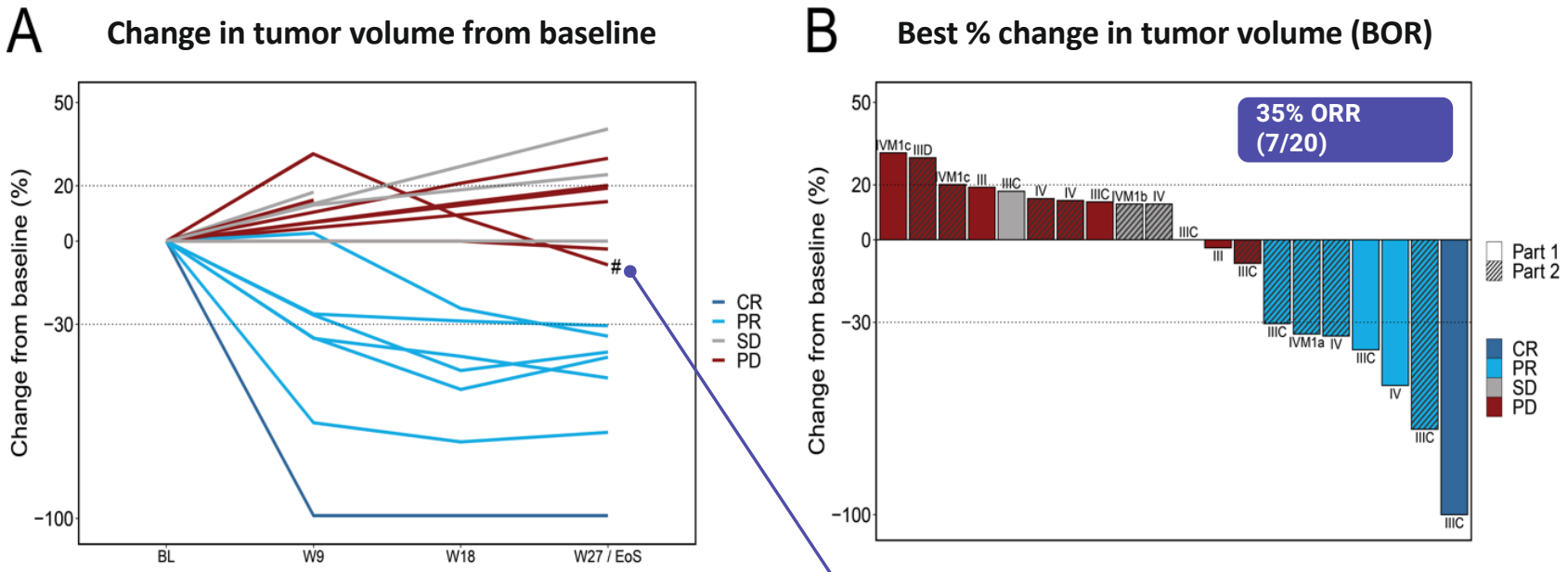


Patients w/DCR vs. PD



- **ONCOS-102 replication** supported in tumors for **at least 6 injections** and **until week 9**
- **Q3W schedule** ensures consistent virus exposure and payload delivery
- **Higher ONCOS-102 levels** in Part 2 correlated with tumor response

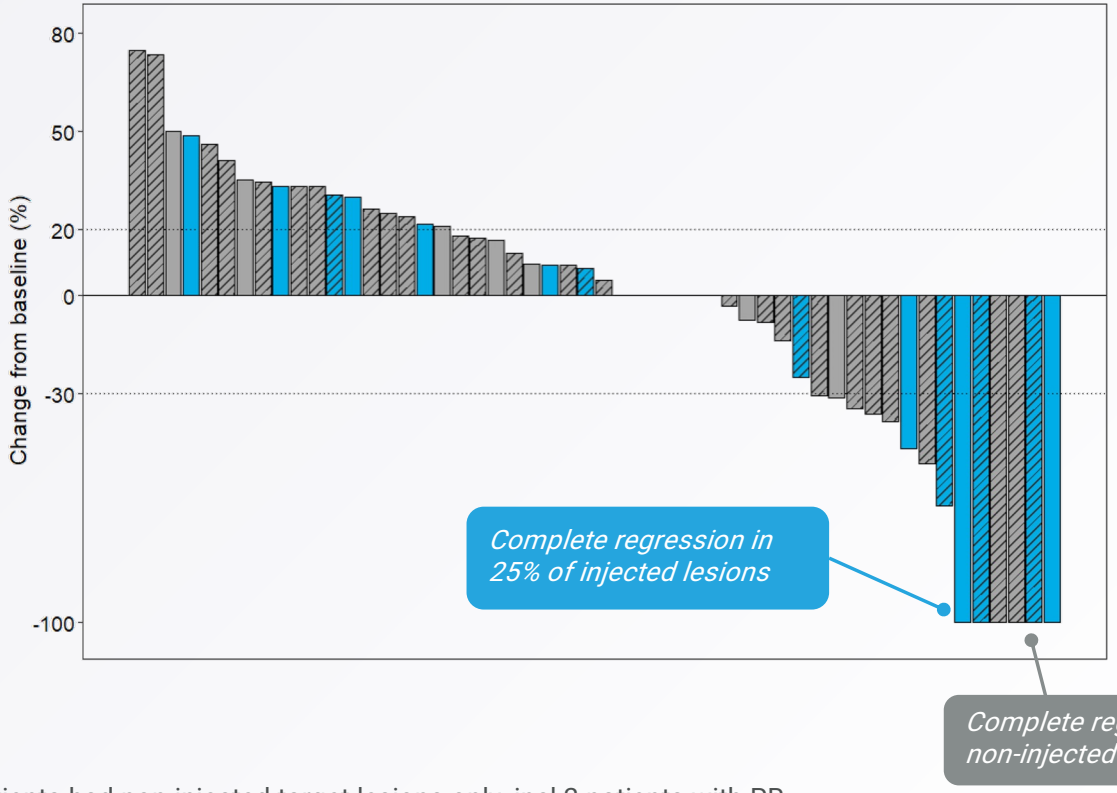
Responders typically had reduction in tumor burden already at the first scan



Multiple examples of systemic (abscopal) effect, including complete regression in non-injected lesions

Response in individual tumors

% change from baseline; injected and non-injected target lesions

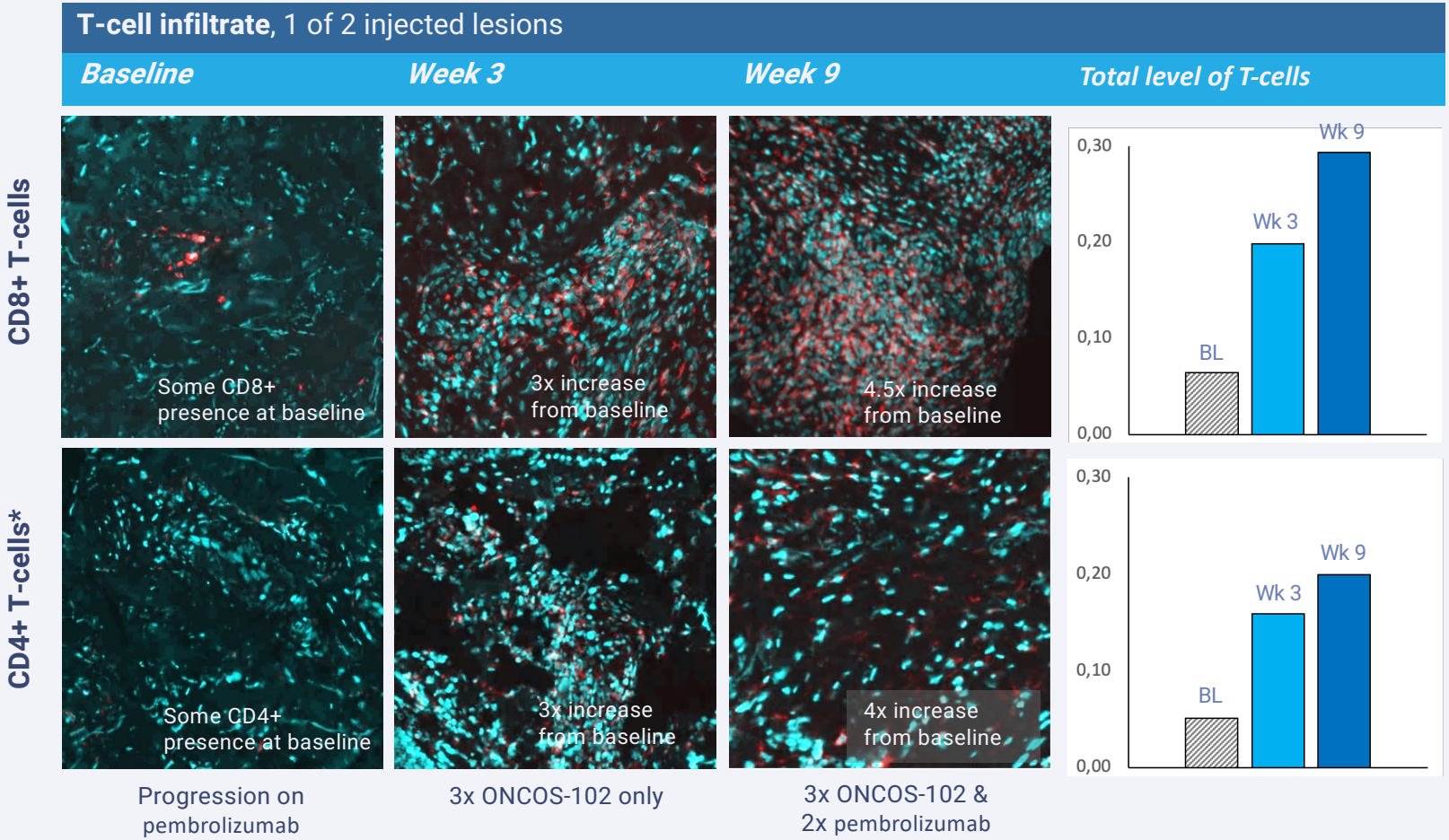


Observed systemic effect:

- **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

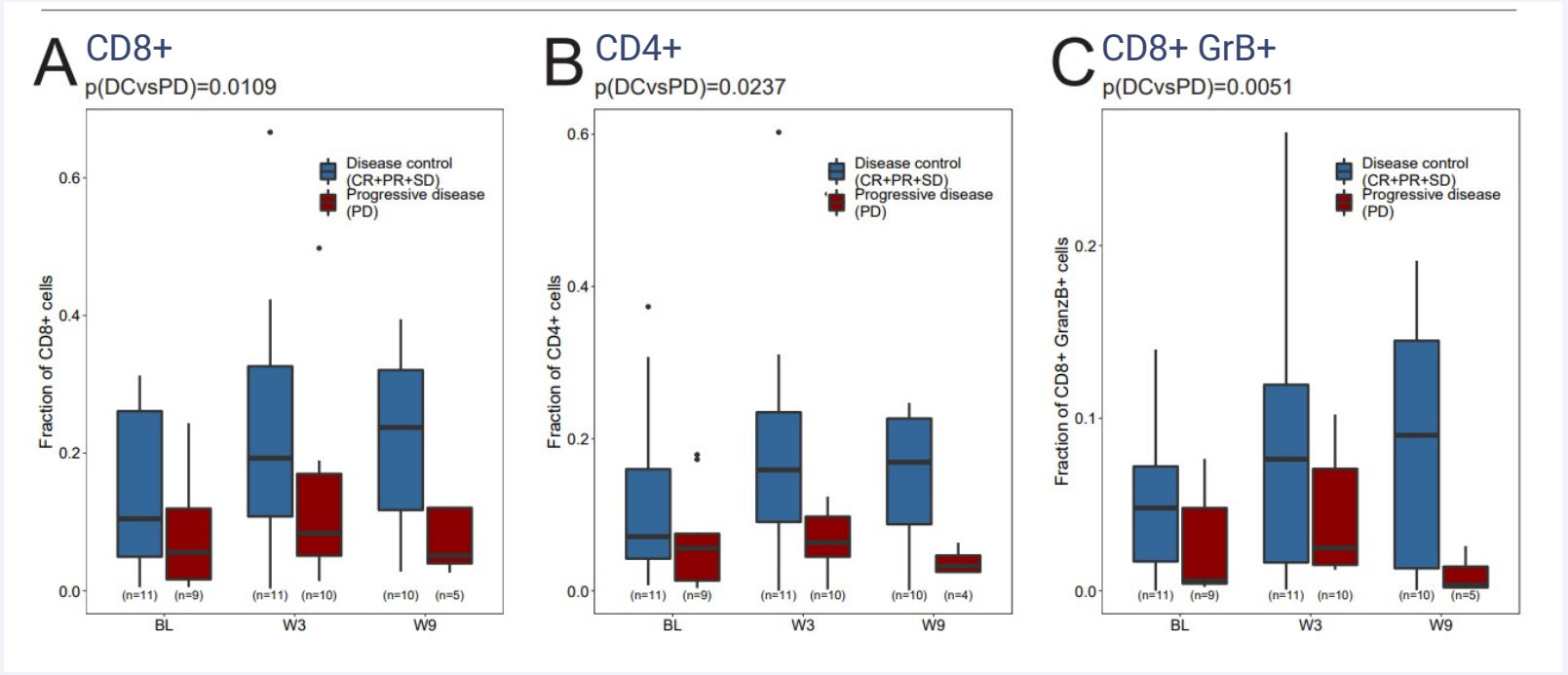
Case Example - partial response patient refractory to t-vec and PD-1 CPI: T-cell infiltration



* FOXP3+ cells (T_{reg}) only present at very low level

Strong increase in T-cell infiltration in patients with clinical benefit (CR+PR+SD)

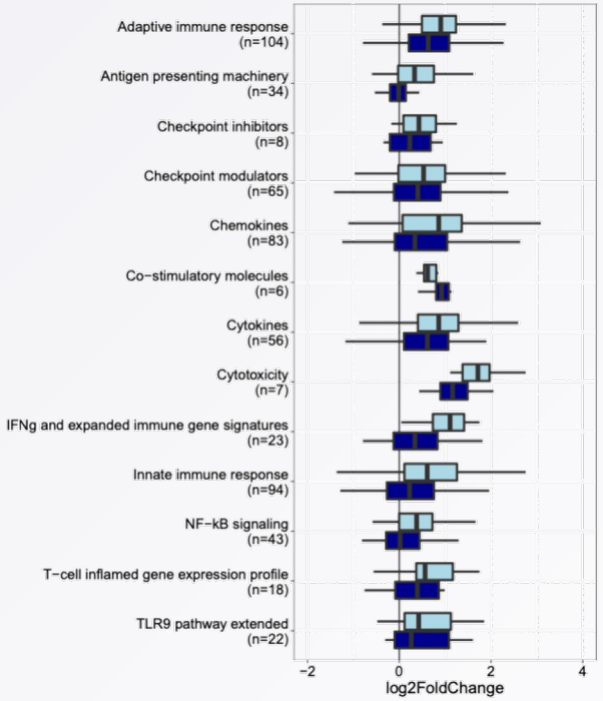
Multiplex immunofluorescence – T-cells



Gene expression data confirms IHC observations and details broad pro-inflammatory tumor re-programing

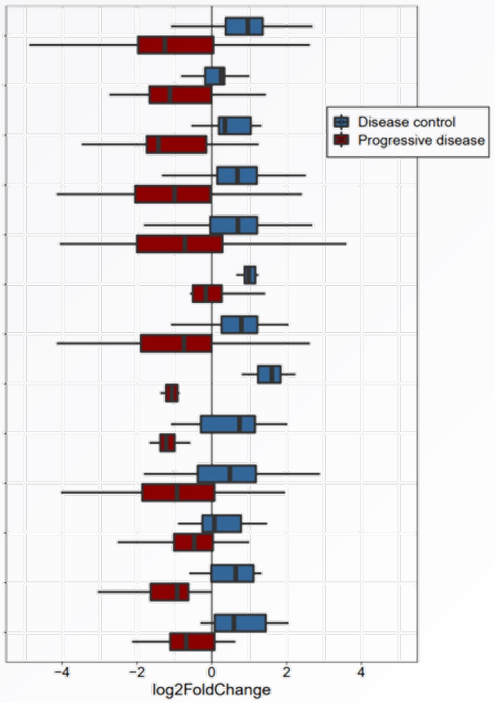
Activation of immune related gene signatures

Week 3 & 9 vs. Baseline



All patients: *Broad activation of immune gene signatures relative to BL*

DCR vs. progression



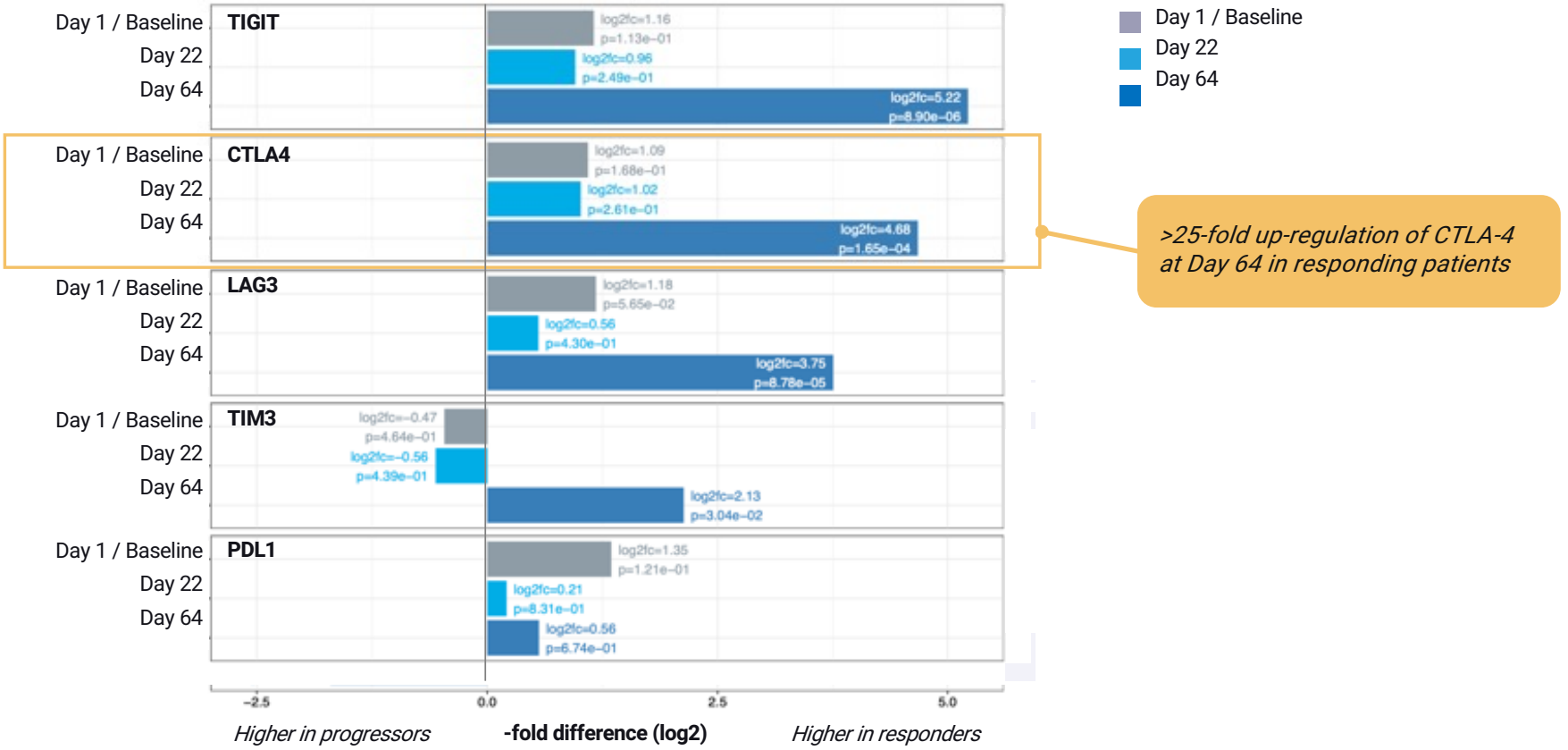
Responders vs. non-responders: *Immune gene activation only persists in responders at week 9*

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**

CTLA-4 is strongly upregulated in response to ONCOS-102

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



>25-fold up-regulation of CTLA-4 at Day 64 in responding patients

Strong rationale for combining ONCOS-102 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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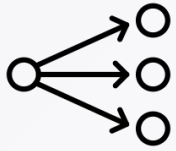

Boost systemic activity

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

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

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