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Anti-tumor potency of cancer vaccine ONCOS-102 in the treatment of malignant mesothelioma in pre-clinical and clinical studies

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Presenter disclosure information

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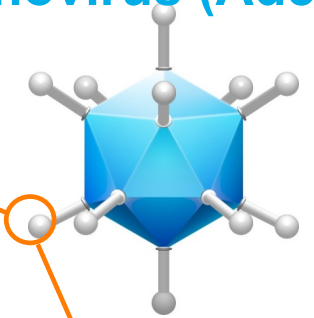
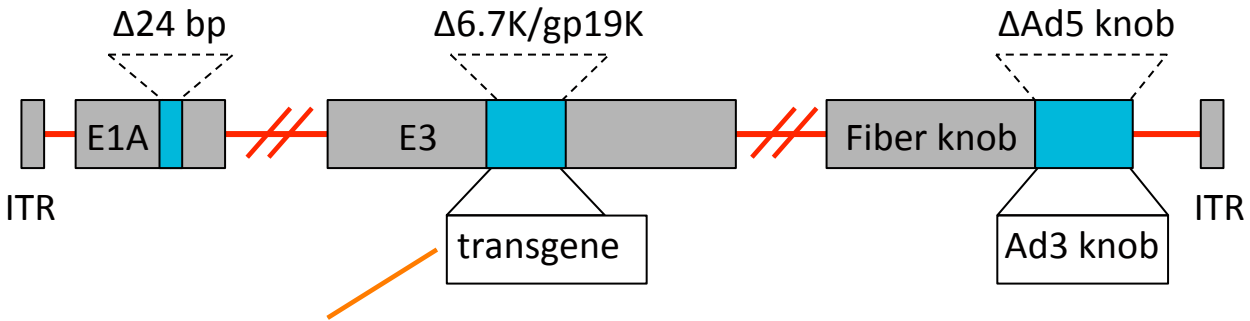
Outline

1. ONCOS-102: rationale for virus construct and mechanism of action
2. Mesothelioma
3. Anti-tumour potency of ONCOS-102 in pre-clinical studies on mesothelioma
4. Clinical study with ONCOS-102 in mesothelioma
5. Summary and take home points

ONCOS cancer immunotherapy platform is based on a purposefully engineered human adenovirus (Ad5)

- Improved infectivity of cancer cells
- Selective replication in cancer cells inducing immunogenic cancer cell death



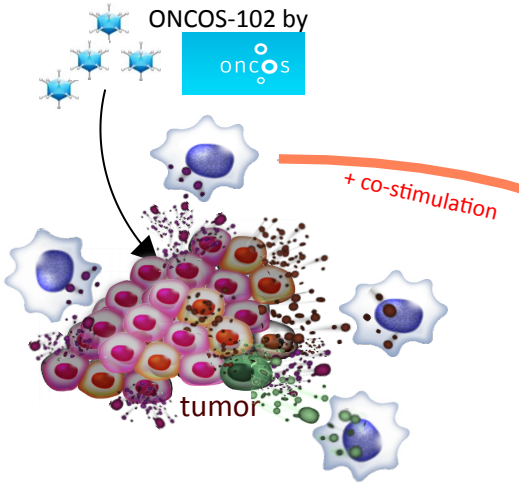


- Transgene expression coupled to virus replication -> expression only in tumor cells
  - GM-CSF transgene in ONCOS-102

ONCOS-102 MoA

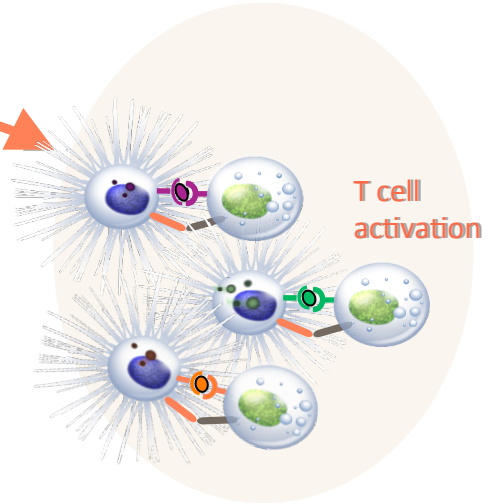
Recognition of threat

Innate Immune System



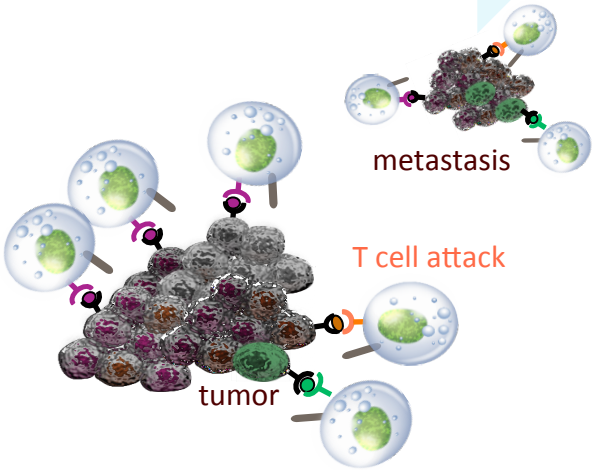
T cell activation

Adaptive Immune System



Immune attack

Anti-tumor Immune Response

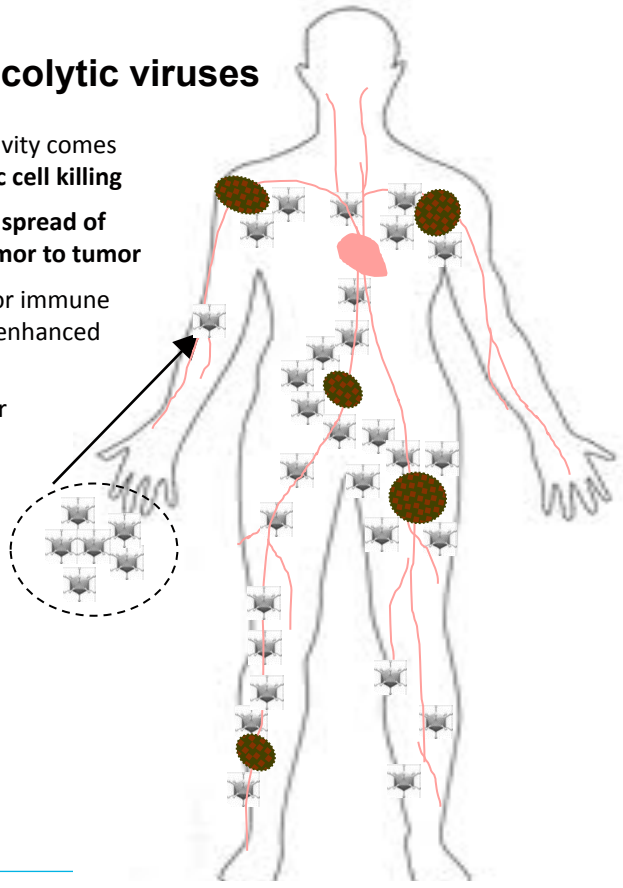


Local ONCOS-102 treatment induces a unique, systemic anti-tumor immune response in every patient = in situ vaccination

Local administration of oncolytic virus may be preferable for optimal immune activation

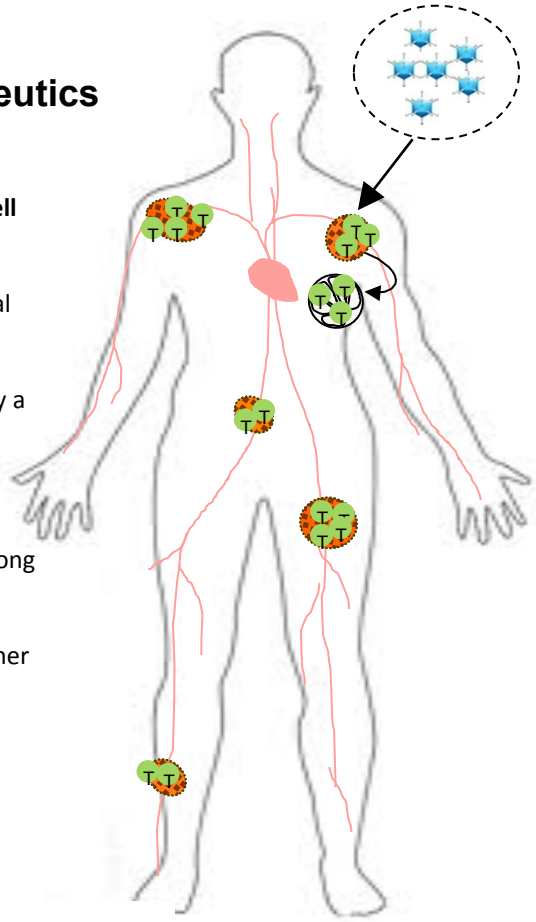
Traditional oncolytic viruses

- Main anti-tumor activity comes **from direct oncolytic cell killing**
- **Requires a systemic spread of <u>active</u> virus from tumor to tumor**
- Virus are modified for immune system evasion and enhanced oncolysis
- Little effect on tumor immunotolerance



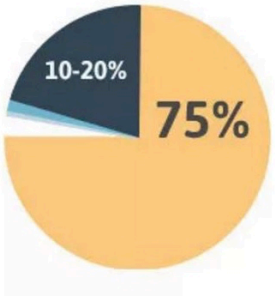
Local immunotherapeutics

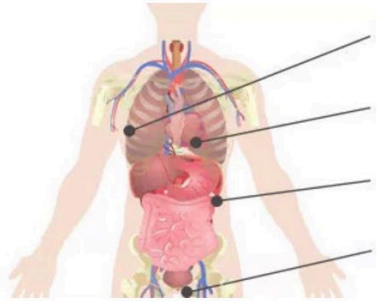
- **Primary anti-tumor activity is a systemic, tumor specific CD8+ T cell attack**
- Local administration utilizes natural immunogenicity of virus
- Immunostimulation is enhanced by a transgene
- Breaks tumor immunotolerance
- Immunological memory provides long term protection
- Potentially sensitizes tumors to other therapies



Mesothelioma

- Malignant mesothelioma is a rare but fatal form of cancer which is difficult to diagnose
- 50.000 people worldwide die from the disease each year
- Latency period longer than 30 years
- median survival time after diagnosis is 9–12 months





Pleural Mesothelioma **75% of all cases**

Pericardial Mesothelioma **1% of all cases**

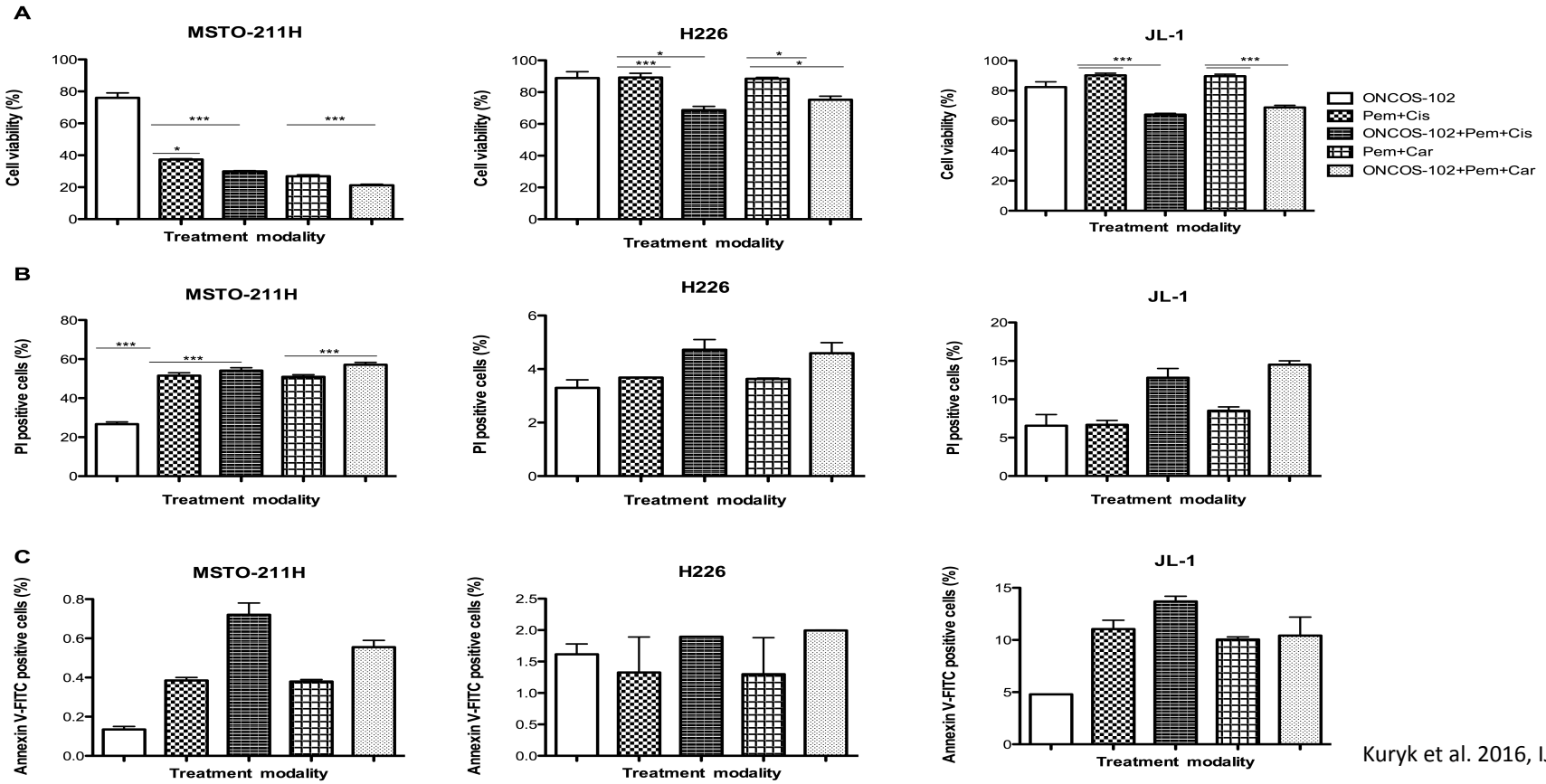
Peritoneal Mesothelioma **10-20% of all cases**

Testicular Mesothelioma **< 1% of all cases**

www.asbestos.com
www.who.int/cancer/en

Anti-tumour potency of ONCOS-102 in pre-clinical studies on mesothelioma

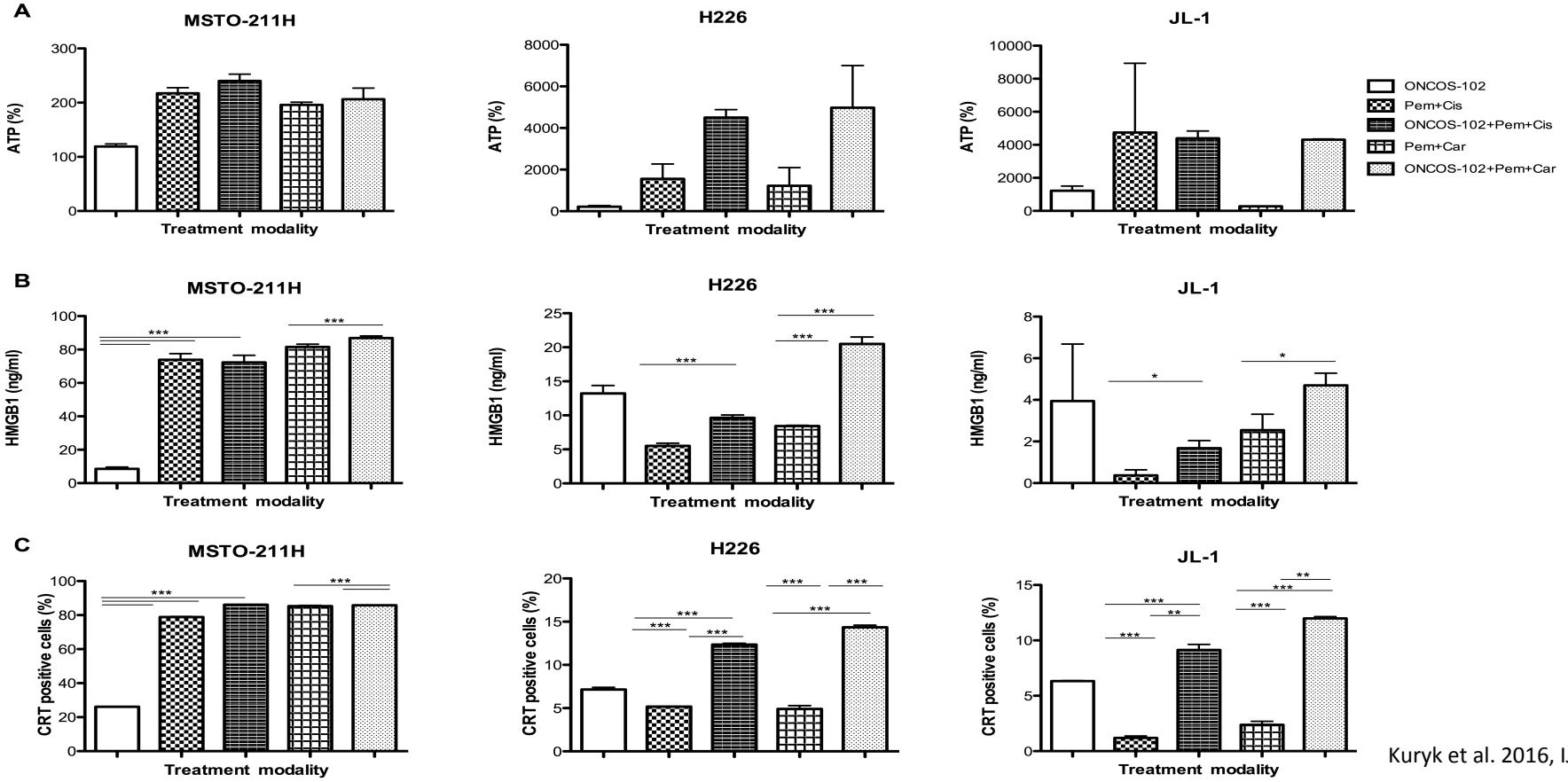
In vitro studies – cell viability, apoptosis/necrosis



Kuryk et al. 2016, IJC

Anti-tumour potency of ONCOS-102 in pre-clinical studies on mesothelioma

In vitro studies – ICD



Kuryk et al. 2016, IJC

Anti-tumour potency of ONCOS-102 in pre-clinical studies on mesothelioma

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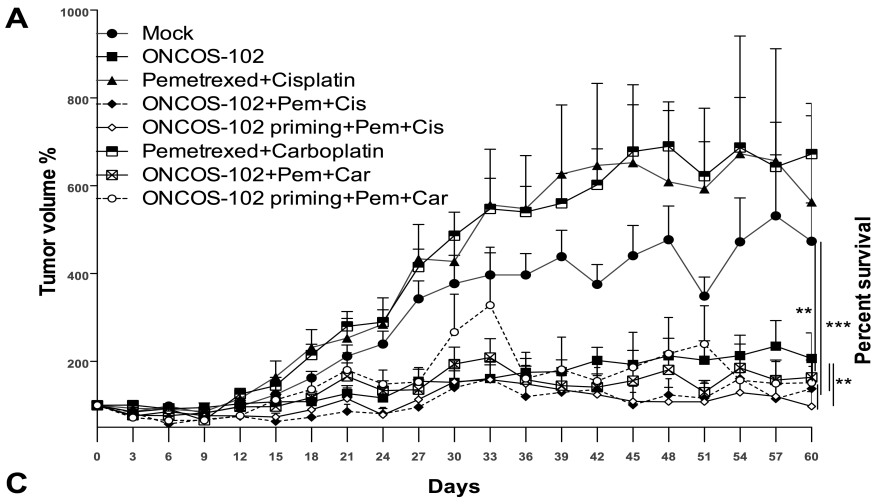
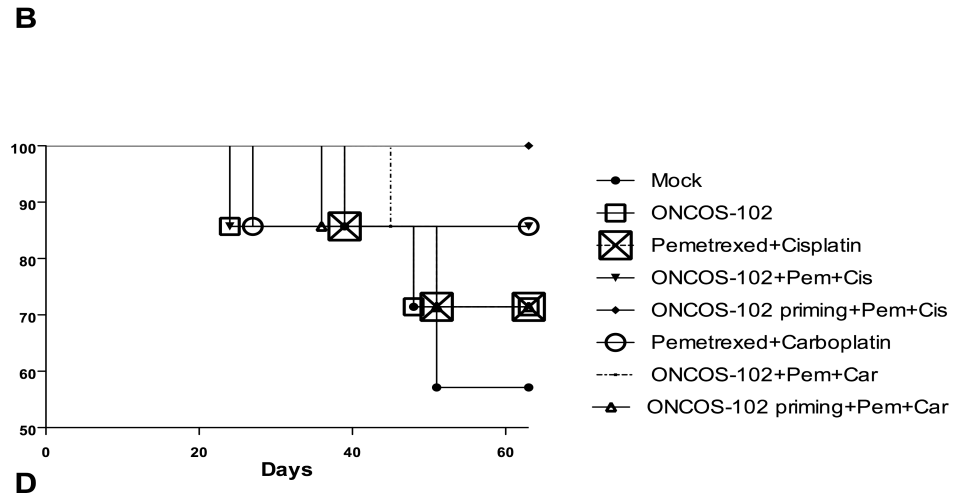
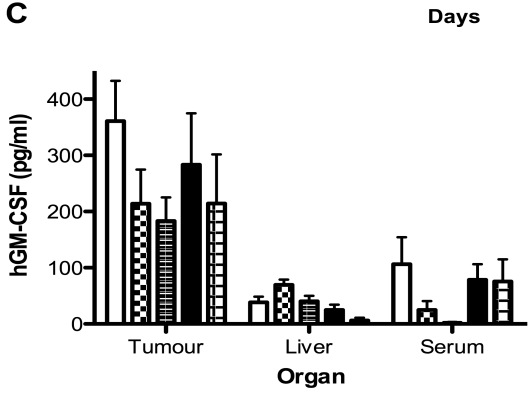
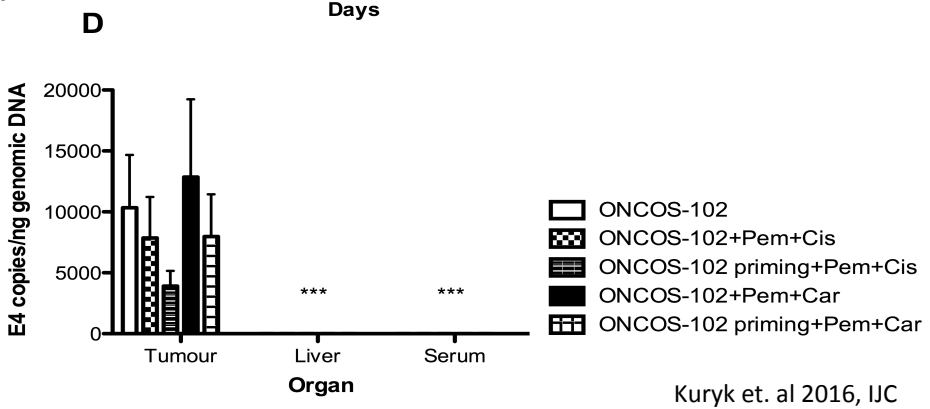
Human Mesothelioma xenograft model in nude mice









Kuryk et. al 2016, IJC

Anti-tumour potency of ONCOS-102 in pre-clinical studies on mesothelioma

Human Mesothelioma xenograft model in nude mice – synergistic effect

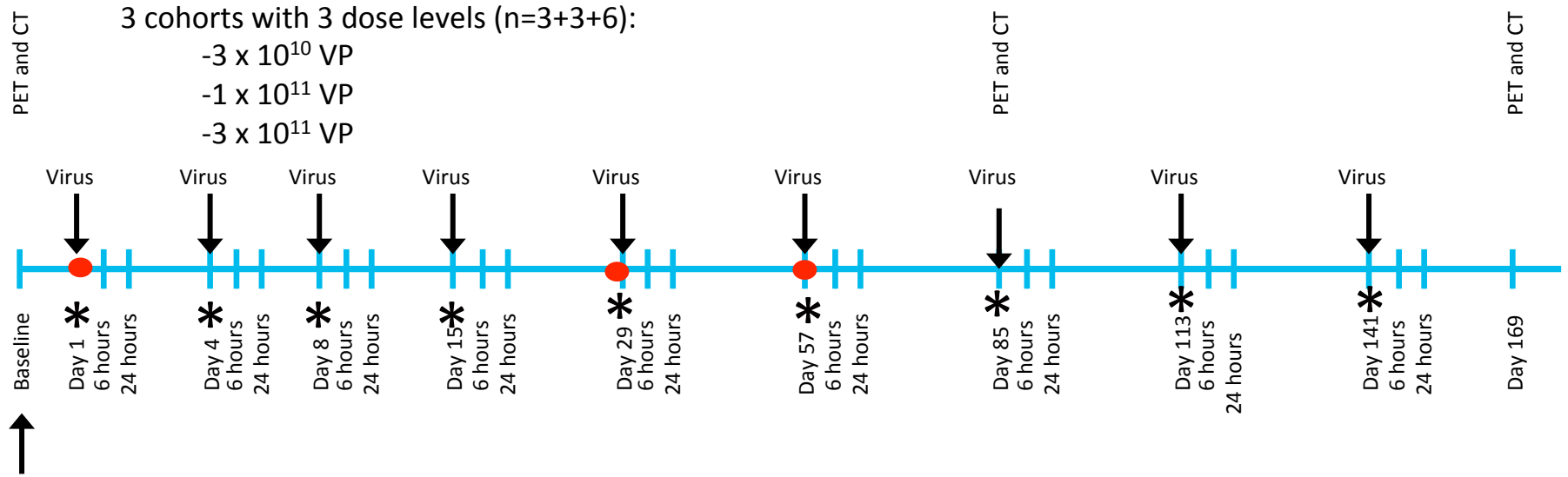
Fractional tumor volume (FTV)								
			ONCOS-102+Pem+Cis			ONCOS-102 prim+Pem+Cis		
Day	Pem+Cis	ONCOS-102	Exp.*	Obs.**	Ratio	Exp.*	Obs.**	Ratio
21	1,12	0,60	0,72	0,40	**1,80**	0,72	0,54	**1,32**
48	1,28	0,45	0,57	0,26	**2,19**	0,57	0,23	**2,50**
60	1,19	0,44	0,52	0,29	**1,78**	0,52	0,20	**2,5**
			ONCOS-102+Pem+Car			ONCOS-102 prim+Pem+Car		
Day	Pem+Car	ONCOS-102	Exp.*	Obs.**	Ratio	Exp.*	Obs.**	Ratio
21	1,32	0,60	0,79	0,79	1,0	0,79	0,85	0,93
48	1,44	0,45	0,64	0,38	**1,70**	0,64	0,46	**1,41**
60	1,42	0,44	0,62	0,35	**1,8**	0,62	0,32	**1,94**

Combined treatment of mesothelioma with ONCOS-102 and Pemetrexed-Cispaltin/Pemetrexed-Carboplatim in BALB/c nude mice. Assessment of therapeutic synergy with FTV calculation method. FTV (mean tumor volume experimental)/(mean tumor volume control). *(Mean FTV of Chemotherapy) x (mean FTV of Virus). **(expected FTV by the observed FTV). A ratio of >1 indicates a synergistic effect, and a ratio of <1 indicates a less than additive effect.

Kuryk et al. 2016, IJC

Clinical study with ONCOS-102

Phase I study (ONCOS-C1) - schedule



Cyclophosphamide (50mg/day) starts

= Blood sample (whole blood, serum)

= biopsy

= PBMC

i.t. +/- intraperitoneal administration over 6 months
Monitoring of disease progression by CT/PET scans in 10 patients

Clinical study with ONCOS-102

40% of evaluable patients showed stabilization of disease after 3 months

Dose cohort	Patient	3 months RECIST / PET (11/12 patients alive)		OS (months)
3 x 10^{10} VP	FI1-01-Ovarian	SD	PMD	9.3
	FI1-02-Colon	SD	MMR	12.7
	FI1-04-Colon	PD	PMD	4.1
1 x 10^{11} VP	FI1-06-Liver	PD	PMD	3.6
	FI1-08-Lung	PD	PMD	5.2
	FI1-09-Mesothelioma	PD	SMD	8.5
3 x 10^{11} VP	FI1-13-Rectum	PD	PMD	9.7
	FI1-14–Mesothelioma	SD	PMD	18.1
	FI1-17 – STS	PD	PMD	11.1
	FI1-19 –Ovarian	SD	SMD	>37 (alive)

SD =Stable disease, PD =Progressive disease, MMR = Minor metabolic response,
SMD =Stable metabolic disease, PMD =Progressive metabolic disease.

Clinical study with ONCOS-102

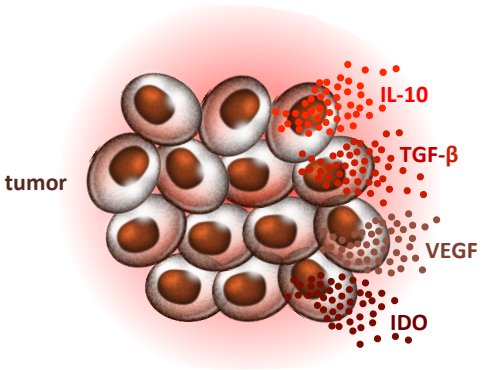
ONCOS-102 is a tumor targeted immune activator making tumors susceptible to immune therapy

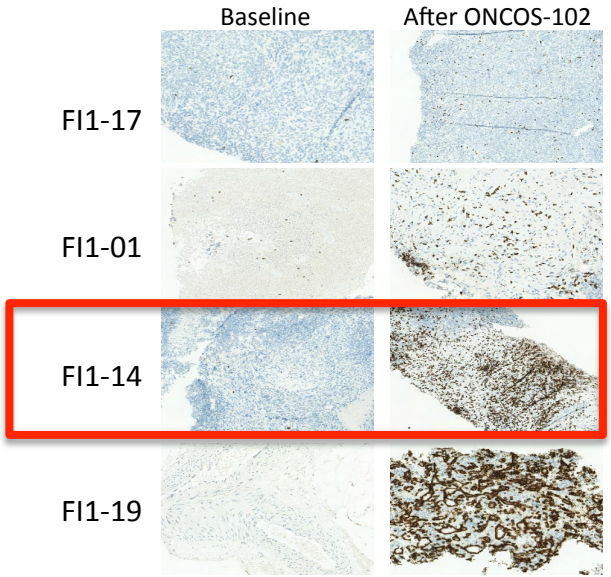
Challenge 1: No immune cells at tumor site

Intratumoral ONCOS-102

ONCOS-102 teaches immune system to recognize tumors and attracts CD8+ T cells into tumors

Tumor-derived factors prevent immune system recognizing cancer cells:
no immune cells at tumor site





Ranki et al 2014, Oncoimmunol.

Clinical study with ONCOS-102

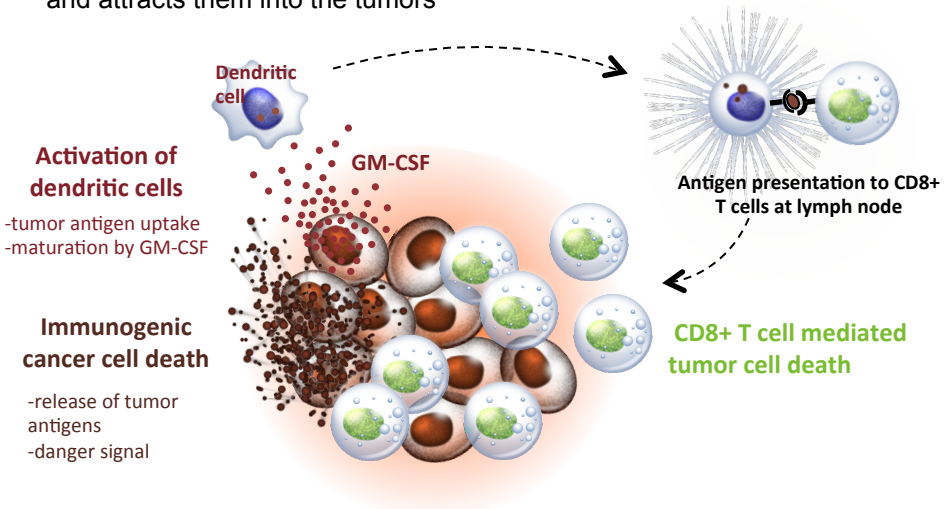
ONCOS-102 is a tumor targeted immune activator making tumors susceptible to immune therapy

Challenge 2: No tumor-specific immunity

Intratumoral ONCOS-102

ONCOS-102 induces tumor specific CD8+ T cells

ONCOS-102 induces tumor specific CD8+ T cells and attracts them into the tumors



Induction of tumor specific CD8+ T cells demonstrated in two patients in Phase I study

Clinical study with ONCOS-102

ONCOS-102 is a tumor targeted immune primer making tumors susceptible to immune therapy

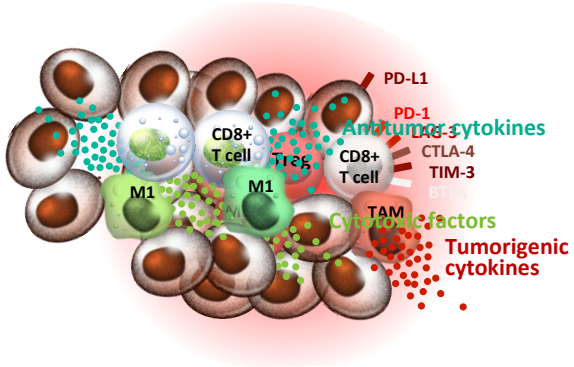
Challenge 3: Immune cells are unable to kill tumor cells

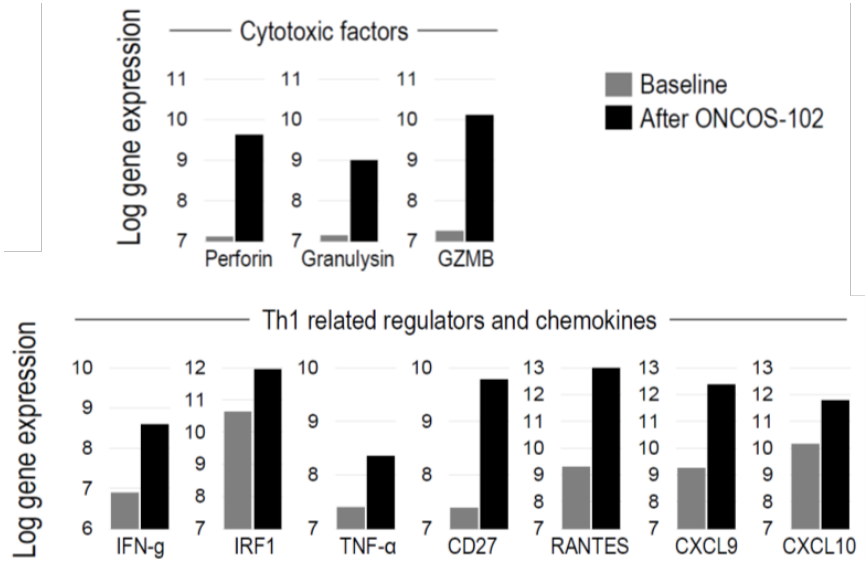
Intratumoral ONCOS-102

ONCOS-102 induces local cytokine environment supporting anti-tumor cellular attack

ONCOS-102 induces cytokine profiles supporting anti-tumor cellular response

Tumor derived factors impair the function of immune cells: **immune cells are unable to kill tumor cells**





Clinical study with ONCOS-102

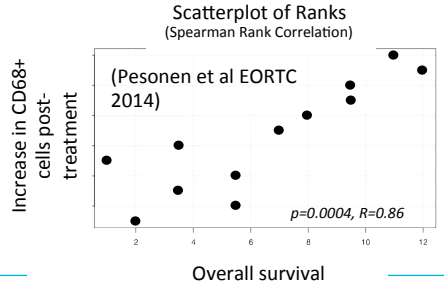
Intratumoral administration of ONCOS-102 induces a systemic CD8+ immune response against tumor antigens in Ph I

Innate Immune System

Recognition of threat

- **Induction of proinflammatory cytokines + fever (all pts)**
- **Infiltration of innate immune cells into tumors in 11 out of 12 pts**
- **Correlation between post-treatment increase in innate immune cells and OS:**

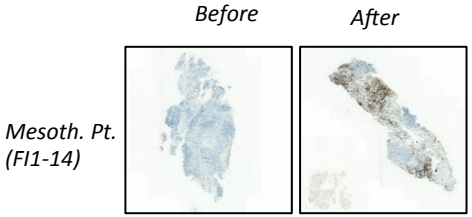
Marker	P-value	Correlation coefficient (R)
CD68	0.0004	0.86
CD163	0.019	0.68
CD11c	0.005	0.75



Adaptive Immune System

Tumor site activation

- **Infiltration of CD8+ T-cells into tumors in 11 out of 12 pts**
- **Cytotoxic molecules expressed by T-cells (perforin, granzyme B)**
- **Correlation between post-treatment increase in CD8+ T cells and OS (p=0.008, R=0.74)** (Pesonen EORTC 2014)
- **CD8+ T-cell infiltration also in non-injected distant metastasis**

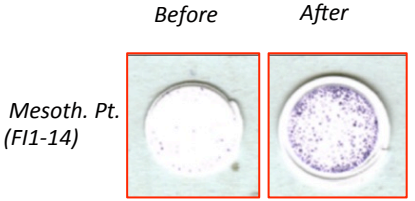


CD8+ T cells increase in tumors after ONCOS-102 treatment

Anti-tumor Immune Response

Immune attack

- **Induction of tumor-specific CD8+ T-cells**
- **Correlated with clinical benefit**



***MAGE-A3* specific CD8+ cells** *were induced by ONCOS-102 (IFN-gamma ELISPOT)*

->47% reduction in total tumor activity (PET)

Ranki et al 2014, Oncoimmunol.

Summary and Take Home Points

- Intratumoral administration of ONCOS-102 to patients with advance solid tumors was safe and has shown clinical benefit
- ONCOS-102 triggers anti-tumor immune responses and development of tumor specific T cells
- ONCOS-102 is a tumor targeted immune activator making tumors susceptible to immune therapy
- There is a rationale for evaluation of ONCOS-102 in combination with other immunotherapies (e.g. CPIs)

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On-going clinical study on mesothelioma (NCT02879669)

A Randomised Phase II Open-label Study With a Phase Ib Safety lead-in Cohort of ONCOS-102, an Immune-priming GM-CSF Coding Oncolytic Adenovirus, and Pemetrexed/Cisplatin in Patients With Unresectable Malignant Pleural Mesothelioma

Purpose of study:

- To assess safety and efficacy of ONCOS-102 in combination with chemotherapy (both 1st and 2nd line treatment)
- To confirm correlation of immune and clinical endpoints

Primary endpoints:

- Safety of ONCOS-102 in combination with chemotherapy

Secondary endpoints:

- Assess tumour specific immunological activation in blood. Assess immunological activation in tumour mass. ORR, PFS and OS