Memorial Sloan Kettering Cancer Center™

Melanoma and oncolytic adenoviruses

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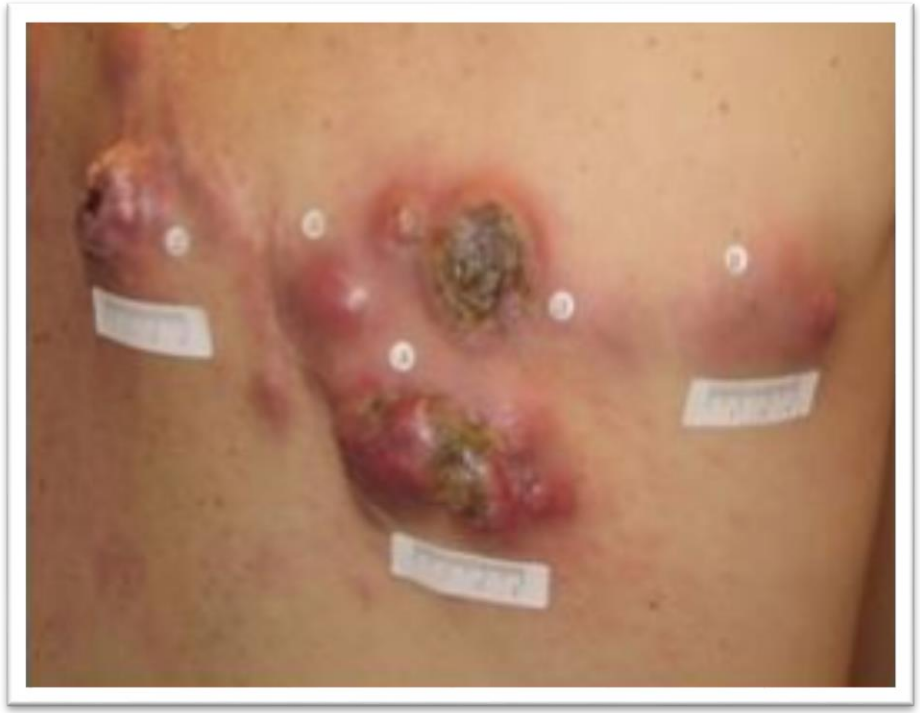
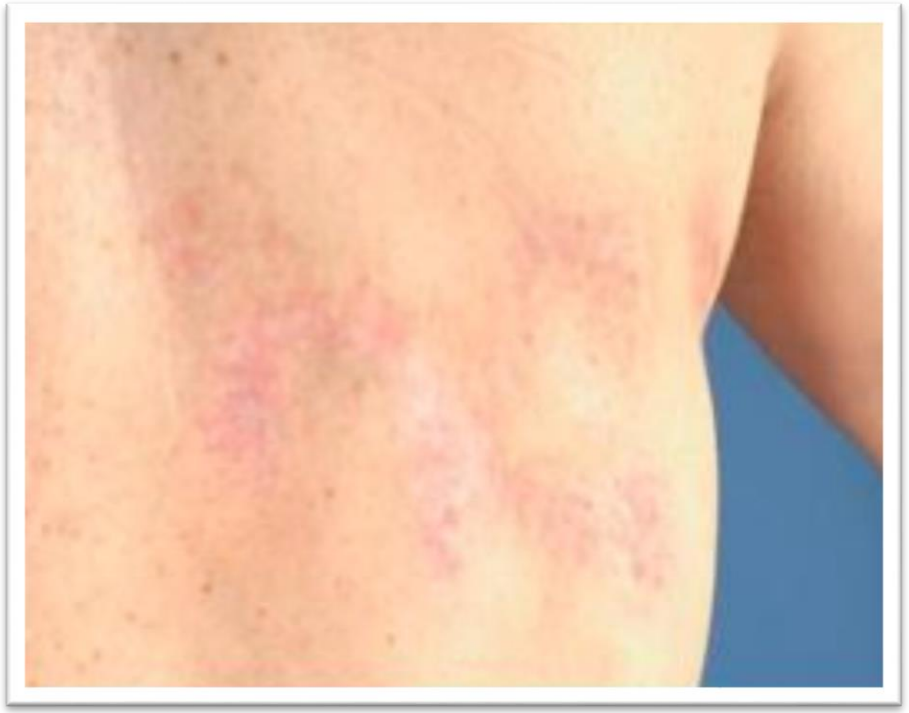
Immunotherapy has revolutionized the treatment of malignant melanoma

Real world example – Patient in an ipilimumab checkpoint inhibitor trial

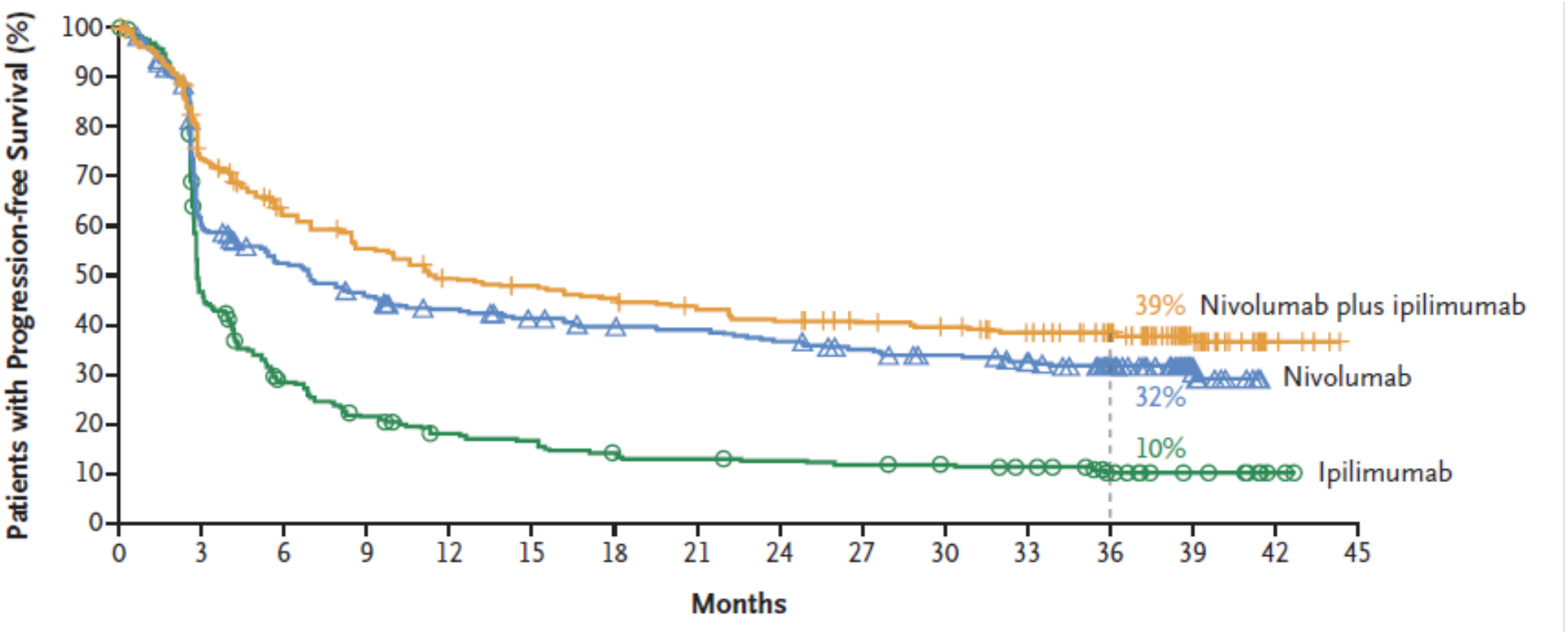


Prior to starting ipilimumab



One year of ipilimumab treatment

PD-1 checkpoints have surpassed CTLA-4, and become the cornerstone of melanoma treatment



PD-1 checkpoint-based therapy in melanoma

Two main checkpoint inhibitor (CPI) treatment choices

- Anti-PD-1 monotherapy: Pembrolizumab or Nivolumab
- Anti-PD-1 + anti-CTLA4 combination therapy: Nivolumab plus Ipilimumab

45 - 60% objective response rate

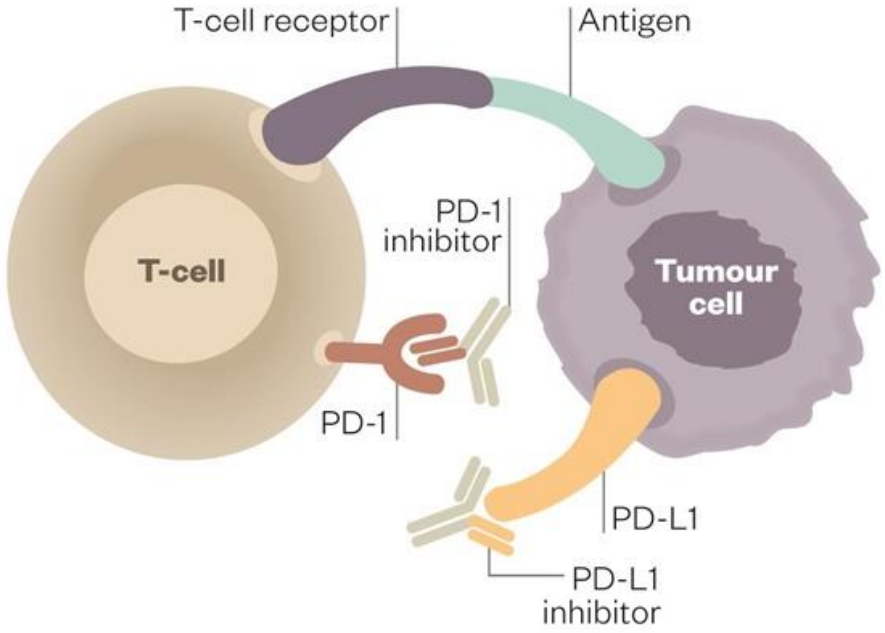
- Responses can last for years, but not forever

Overactive immune system leads to immune-related adverse events (irAEs)

- Diarrhea / Colitis
- Liver inflammation
- Pneumonitis
- Thyroid, Pituitary dysfunction

irAE rate varies by mono- versus combination CPI therapy

- CPI monotherapy: 1 in 4 require steroids
- CPI combination: 3 in 4 require steroids



However, most patients still become resistant to anti-PD-1 treatment

Standard options post PD-1

After PD-1 monotherapy

- BRAF-MEK, if V600 mutant
- Nivolumab plus ipilimumab
- Ipilimumab alone
- Cytotoxic chemotherapy
- T-VEC if injectable

After PD-1/CTLA4 combination therapy

- BRAF-MEK, if V600 mutant
- Cytotoxic chemotherapy
- T-VEC if injectable

If local progression only

- Surgery
- Radiation therapy

Non-standard options post PD-1

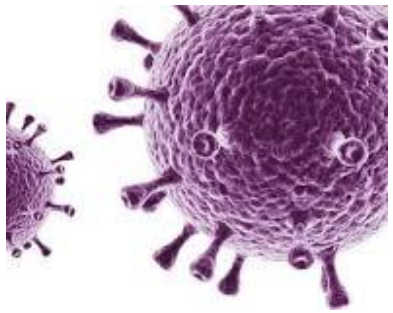
Clinical Trials (selected)

- PD-1 combination with:
  - Oncolytic virus
  - TLR9 agonist
  - Neoantigen vaccines
  - HDAC inhibitor
  - OX40 agonist
  - LAG-3 inhibitor
- Tumor Infiltrating Lymphocyte (TIL) trials

Off-label uses

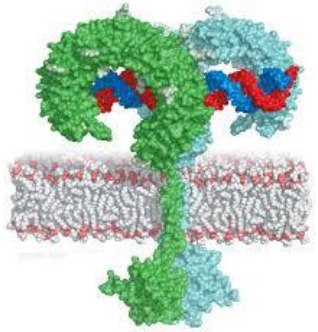
- BRAF + MEK + PD-1
- T-VEC + PD-1 inhibitor
- Radiation + PD-1 +/- Ipilimumab

Promising experimental therapies available for PD-1 resistant patients



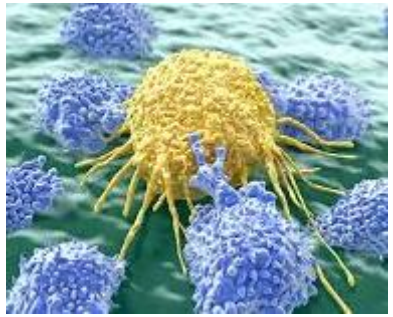
Oncolytic viruses

- Trigger oncolysis and inflammatory response
- Turn cold tumors hot
- Trials ongoing in combination with PD-1 and CTLA-4



TLR-9 agonists

- Stimulate innate immune response via TLR-9 signaling
- Trials ongoing in combination with PD-1 and CTLA4



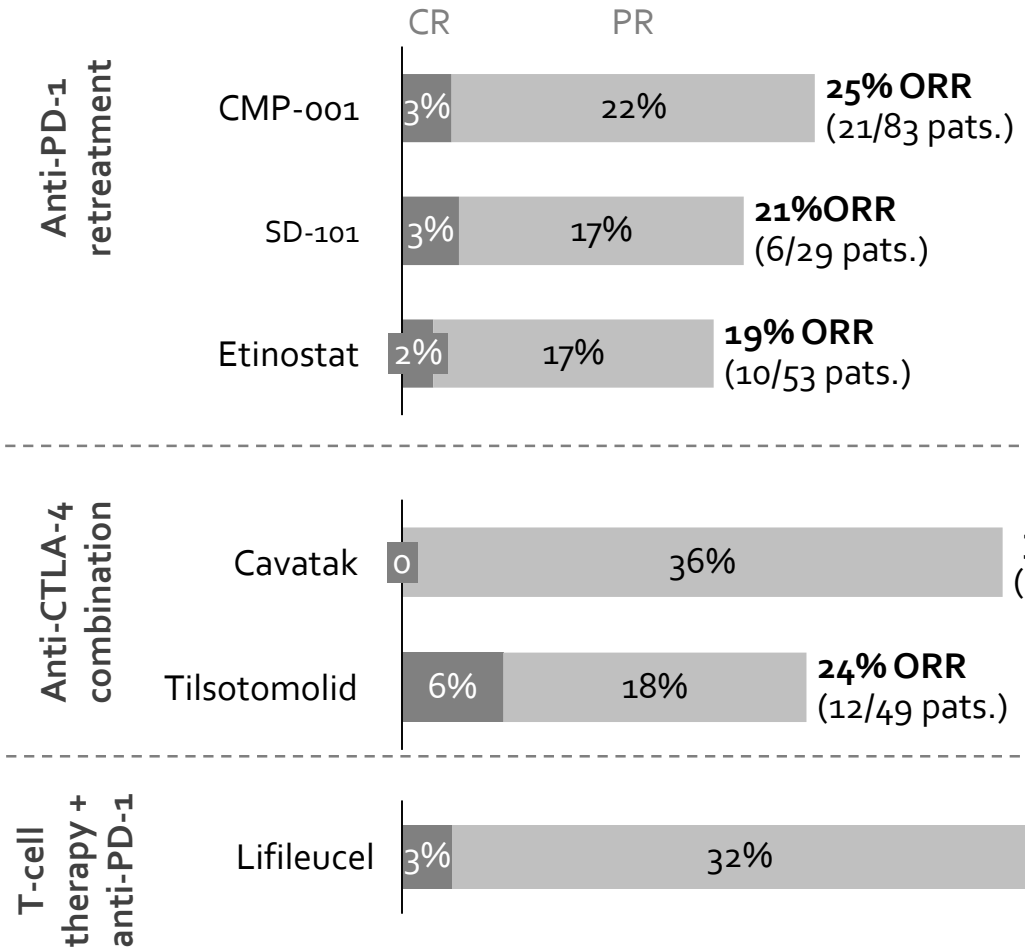
TIL therapy

- Autologous T-cells harvested from the patient's tumor
- Combination trials ongoing with systemic immune activators (eg IL2)
- Potentially efficatious, but significant cost and logistics hurdles

Neoantigen vaccines

- Trigger T-cell responses to shared or personalized neoantigens
- Provide tumor targets to T-cells
- Trials ongoing with PD-1

Response rates reported in anti-PD-1 refractory melanoma phase I / II trials



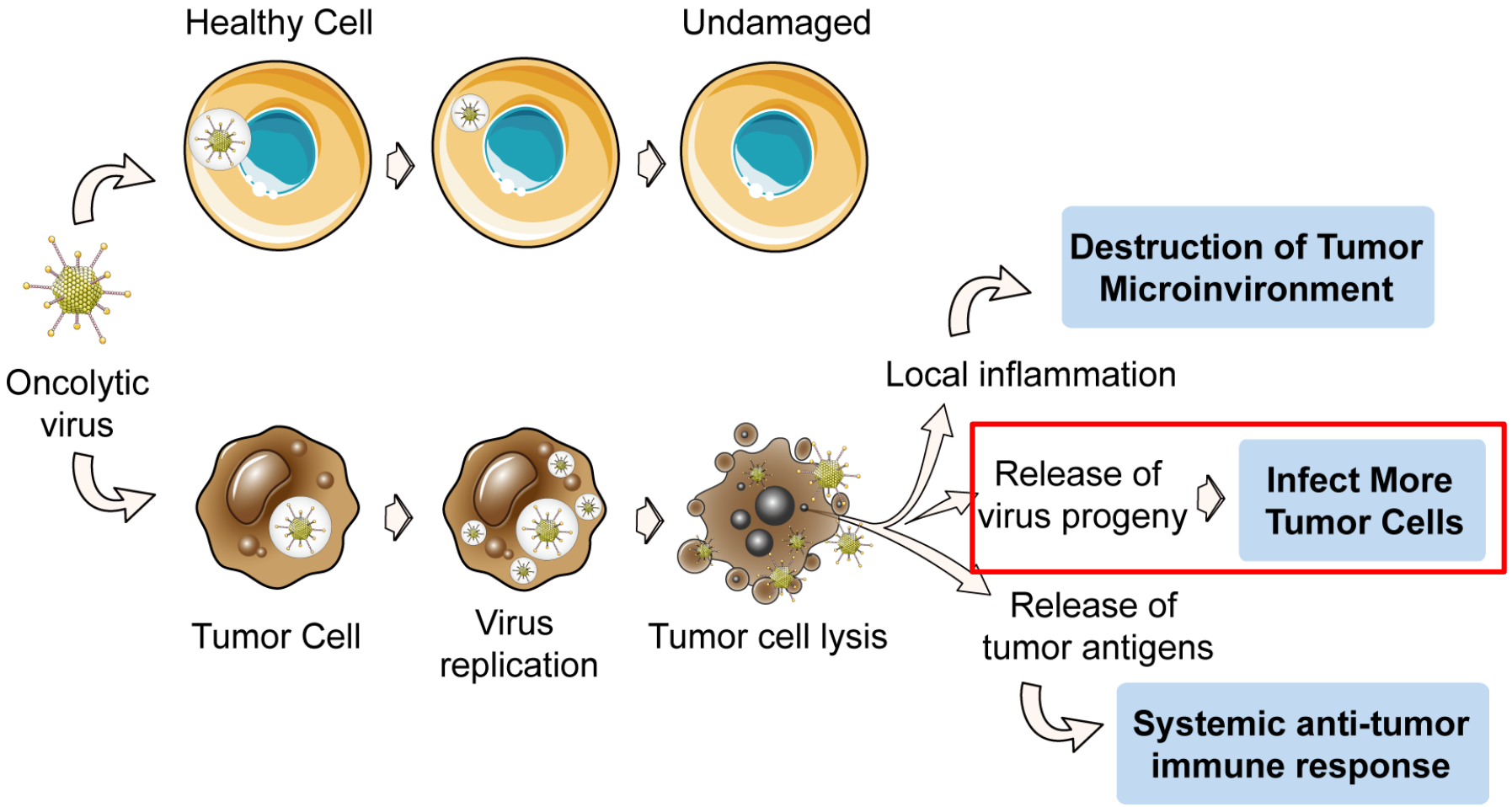
Comment

- *Checkmate Pharma, TLR-9 agonist*
- *Data from high dose cohort*
- *Dynavax, TLR-9 agonist*
- *Syndax Pharma, HDAC inhibitor*

Most pats CTLA4 naïve, 10-20% ORR expected

- *Merck (Viralytics), Oncolytic virus, up to 20 injections*
- *Idera, TLR-9 agonist*
- *IOvance, autologous TIL therapy with IL-2*
- *Complex and expensive manufacturing*

How oncolytic viruses work



Overview of the most common oncolytic virus classes

Virus type	Description	Pros	Cons
Vaccinia virus (130-280kb)	Large enveloped DNA viruses, with ability to carry long payload DNA sequences	Well known vector, large DNA payload capacity, extra-nuclear replication	Complex CMC, large size, slow replication
Herpes virus (120-200kb)	Large enveloped DNA viruses, with ability to carry long payload DNA sequences	Only approved OV virus class, highest DNA payload capacity	Weak innate immune response, long latency, long/permanent infec-tivity, complex CMC
Adenovirus (35-40kb)	Mid-size non-enveloped DNA viruses, with ability to carry some payload DNA sequences	Well tolerated, TLR9 agonist, innate immune activator, payload DNA	Not suitable for IV in naked form, less payload DNA than herpes/vaccinia
Small RNA viruses (5-30kb)	Small RNA genome, usually non-enveloped, limited ability to carry transgenes (except VSV)	High oncolytic potency, rapid replication, strong innate response, simple CMC	Safety issues seen with too potent lysis (VSV virus), limited platform versatility

There is a range of oncolytic viruses in clinical development

Company		Asset/ Program	MoA	Highest Phase
AMGEN	H	Imlygic	HSV with GM-CSF transgene, IT only	Approved 2015 as mono Phase III PD-1 combo
MSD	R	Cavatak	Coxsackievirus, non gene modified, IT focus, IV and IP trial ongoing	Phase II
DNAtrix	A	DNX-2401	Chimeric Ad5/3, no transgene, IT and intra-arterial	Phase II
targovax	A	**ONCOS-102**	**Chimeric Ad5/3 with GM-CSF transgene, IT and IP administration**	**Phase II**
Cold Genesys	A	CG0070	Ad5 with GM-CSF transgene, intravesical	Phase II
ONCOLYTICS BIOTECH INC	R	Reolysin	Reovirus, non gene modified, IV only	Phase II
PsiOxus THERAPEUTICS	A	Enadenotucirev	Chimeric Ad5, no transgene, IV only	Phase I/II
Replimune	H	RP1	HSV with GM-CSF, GALV, and ipilimumab transgenes, IT only	Phase I/II
LOKON	A	LOAd703	Chimeric Ad5/35 with TMZ-CD40L and 4-1BBL transgenes, IT only	Phase I/II
VYRIAD	R	Voyager V1	VSV virus with NIS and human interferon beta transgenes, IV only	Phase I
WESTERN ONCOLYTICS	R	Ad-MAGEA3	Maraba virus with MAGEA3 transgene, IV and IT	Phase I
Boehringer Ingelheim	R	VSV-GP	Chimeric VSV virus, IV only	Pre-clinical
TURNSTONE BIOLOGICS	V	WO-12	Vaccinia virus armed with TRIF and HPGD transgenes, IV only	Pre-clinical
transgene	V	Invir.IO	Vaccinia virus platform armed with CTLA-4 ++, solid tumors	Pre-clinical
Oncorus	H	oHSV	Herpes virus with multiple transgenes (PD-1, CTLA4 ++), IT only	Pre-clinical

A *Adenovirus* H *Herpes virus* V *Vaccinia virus* R *RNA virus*

SITC 2019
Gaylord National Hotel & Convention Center Nov. 6-10
NATIONAL HARBOR, MARYLAND

A pilot study of engineered adenovirus ONCOS-102 in combination with pembrolizumab in checkpoint inhibitor refractory advanced or unresectable melanoma

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- Immunocore
- Xcovery
- AstraZeneca

Outline

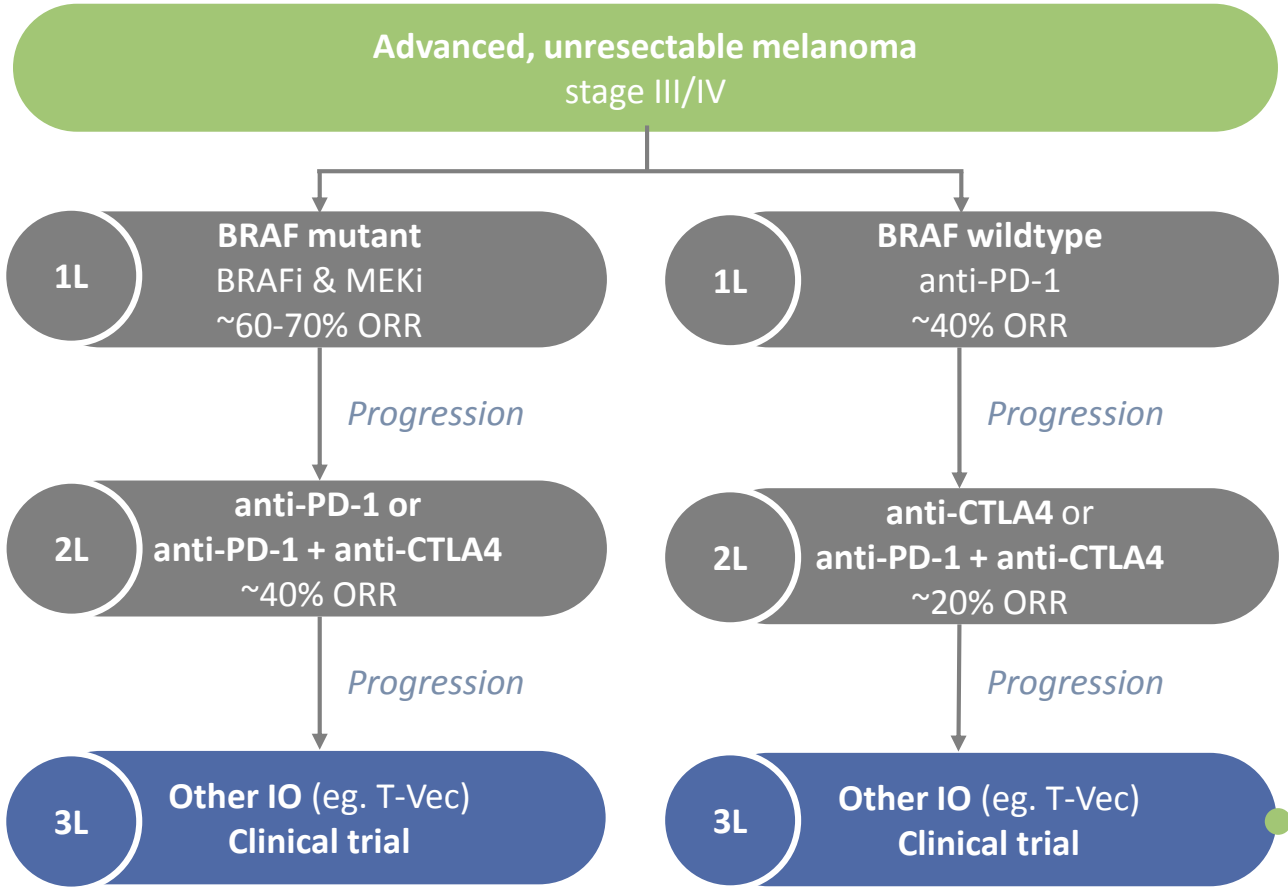
Background and Study Design

Safety of ONCOS-102 + pembrolizumab

Clinical Responses in Part 1

Systemic and Local Immune Responses in Part 1

Limited treatment options for anti PD-1 refractory melanoma



anti-PD-1 **refractory population**

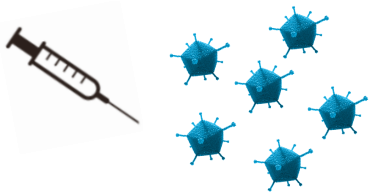
No / few treatment alternatives, high unmet medical need

Poor response rates, typically ORR < 20%

Rationale for priming agent / oncolytic virus in combination with anti-PD-1

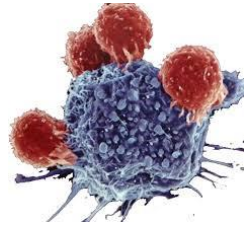
ONCOS-102 is an oncolytic adenovirus serotype 5 armed with a GM-CSF transgene

1 **Virus injection**
Intra-tumoral



2 **Oncolysis**
Immune activation

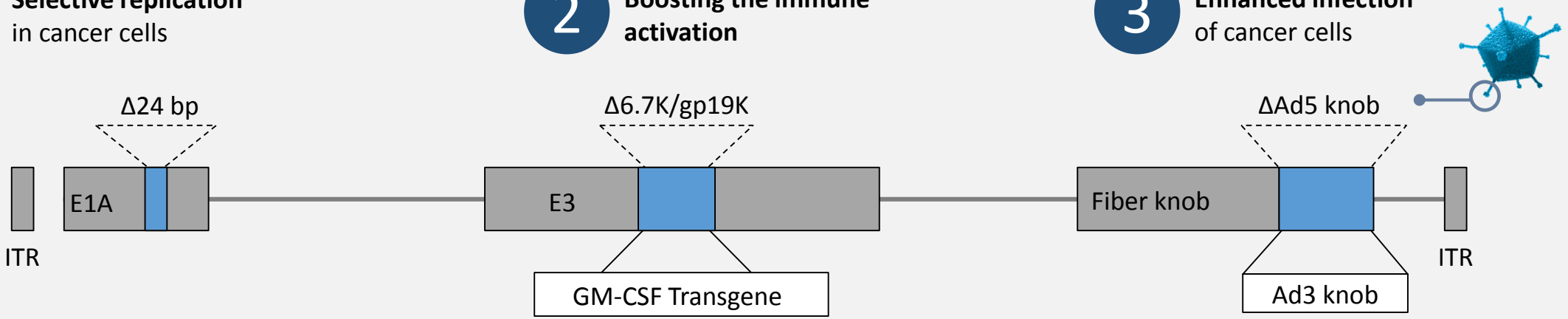
3 **T-cell response**
Anti-tumor immunity



1 **Selective replication** in cancer cells

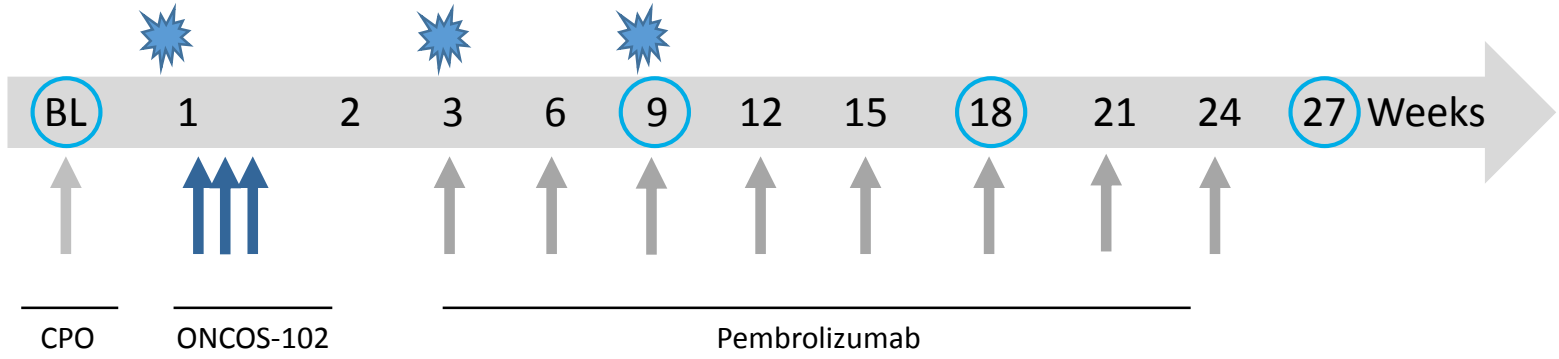
2 **Boosting the immune activation**

3 **Enhanced infection** of cancer cells

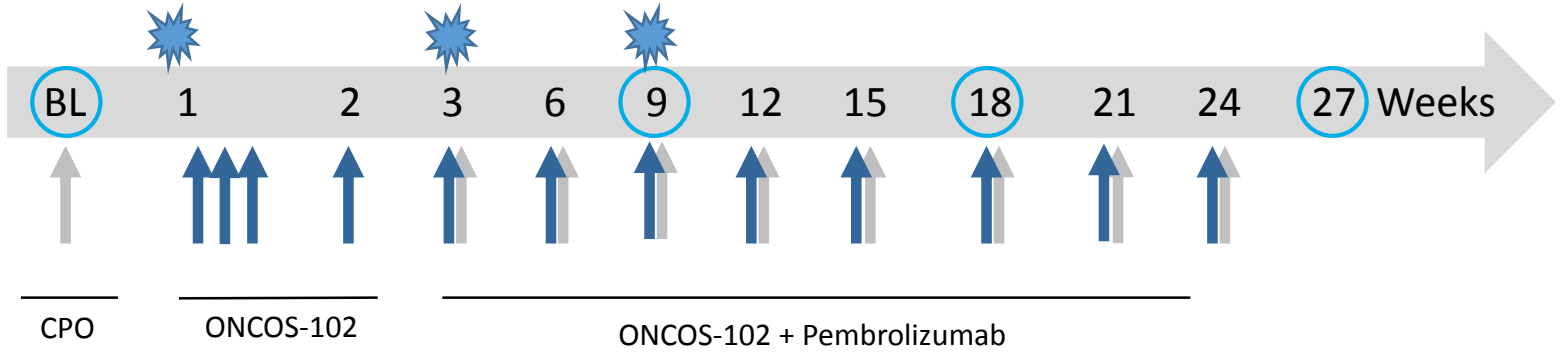


Study Design

Part 1
3x ONCOS-102
8x pembrolizumab
enrollment completed



Part 2
3x ONCOS-102
8x ONCOS-102 + pembrolizumab
enrolling



Imaging

CPO: Cyclophosphamide

Biopsy

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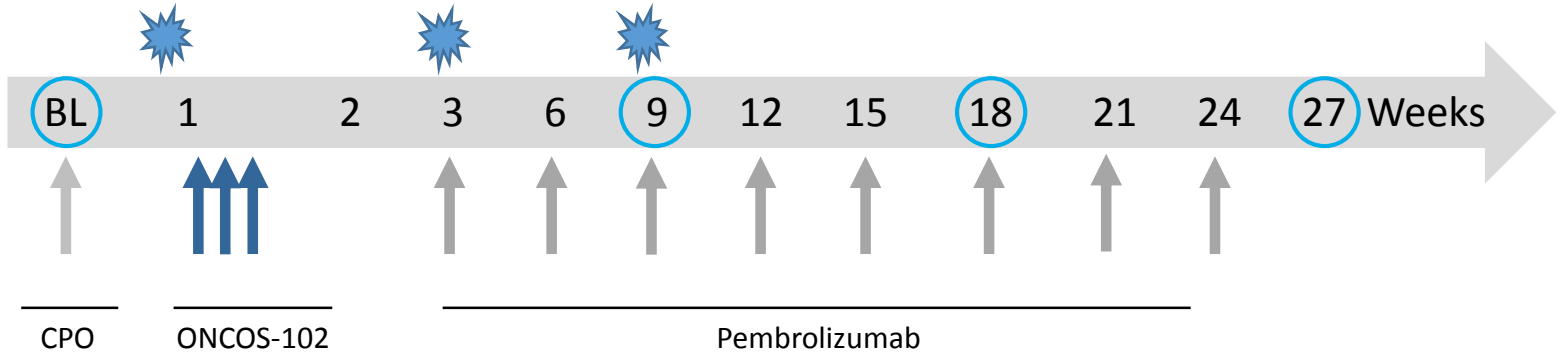

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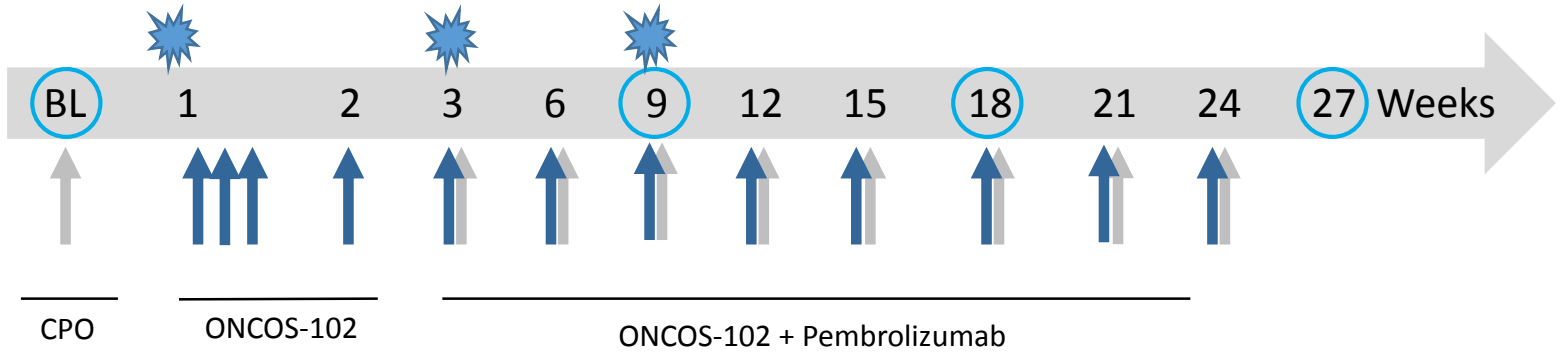


Imaging

CPO: Cyclophosphamide

Biopsy

Demographics and prior treatment

Parameters	Number of patients (n=9)
Age (Y) median (range)	73 (40 – 87)
Gender, n Female Male	 4 5
Histological type Cutaneous Acral	 8 1
Stage at enrollment III IV	 6 3

Prior therapy	Number of patients (n=9)
Systemic Therapy	
anti-PD-1 checkpoint inhibitor Pembrolizumab and/or Nivolumab	9
anti-CTLA4 checkpoint inhibitor Ipilimumab	4
Oncolytic virus Talimogene-laherparepvec	3
BRAF/MEK inhibitors Dabrafenib + Trametinib	2
TLR9 agonist CMP-001 (investigational)	1
Interleukin-2 immunotherapy	1
Surgery	7
Radiotherapy	1
Chemotherapy	1

Preliminary data

Adverse Events *

Adverse Event Prefered term	No. of events	No. of patients	CTCAE grade	Relationship to study drug
Chills	7	5	1, 2	ONCOS-102
Myalgia	6	3	1	
Pyrexia	5	3	1, 2	
Diarrhoea	4	3	1	
Nausea	3	3	1	
Alanine aminotransferase increased	2	2	1	
Fatigue	2	2	1, 2	
Vomiting	2	2	1	
Rash maculo-papular	2	2	1	
Injection site pain	2	1	1	
Injection site swelling	1	1	2	
Peripheral oedema	1	1	2	
Infectious colitis	1	1	3 **	
Productive cough	1	1	2	Pembrolizumab
Haemolytic anemia	1	1	3 **	
Diarrhoea	2	2	1,3 **	
Diabetic ketoacidosis	1	1	4 **	ONCOS-102 and pembrolizumab
Type 1 diabetes mellitus	1	1	4 **	

* AEs occurring in 2 or more Patients or grade 2 or higher

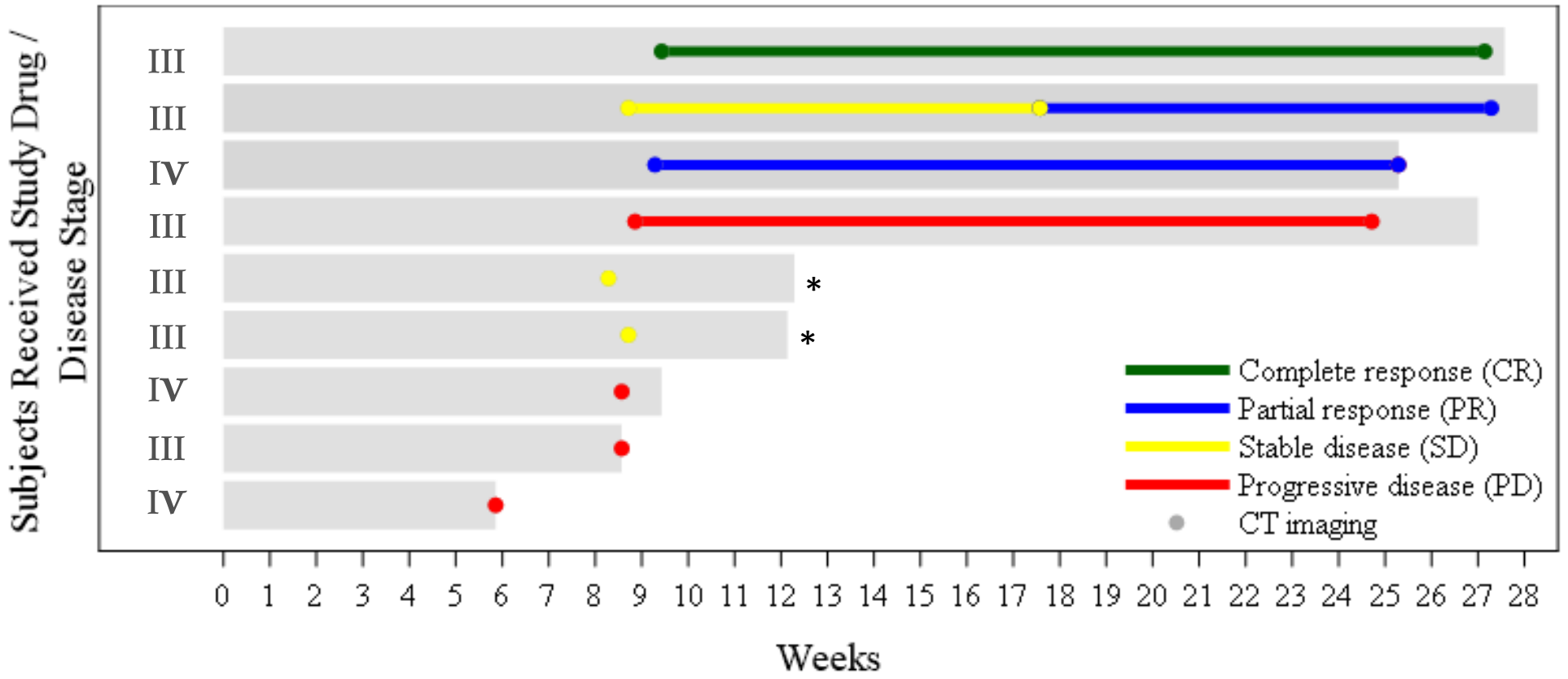
** SAEs

Total no. of AEs reported: 58 in 9 patients

Preliminary data

Objective Response Rate of 33% (3 of 9 pts)

RECIST 1.1

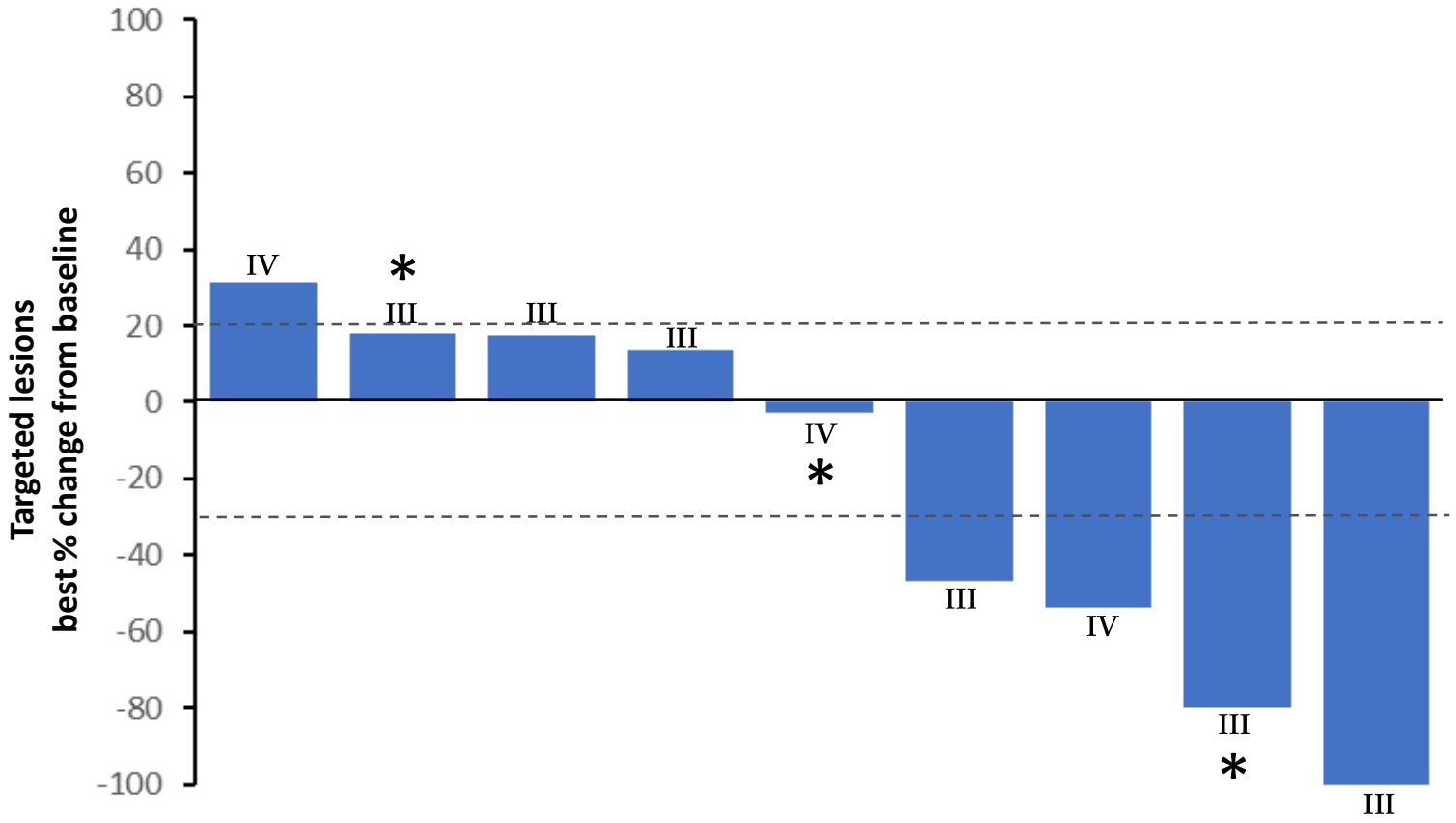


Length of grey bars indicate time from first ONCOS-102 injection to discontinuation/EoS

* Withdrawn due to clinical PD

Preliminary data

Targeted lesions: best % change in tumor burden from baseline



* Non-target Progression of Disease

Preliminary data

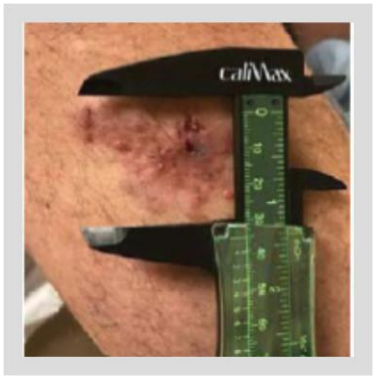
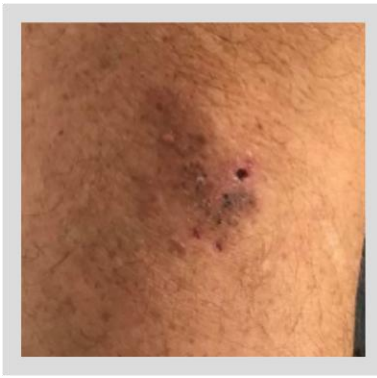
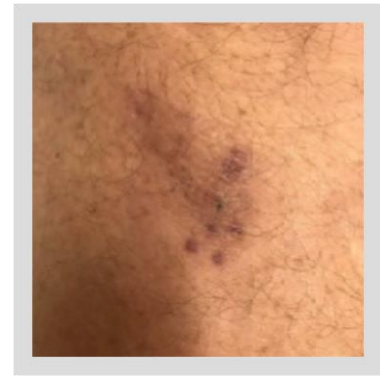
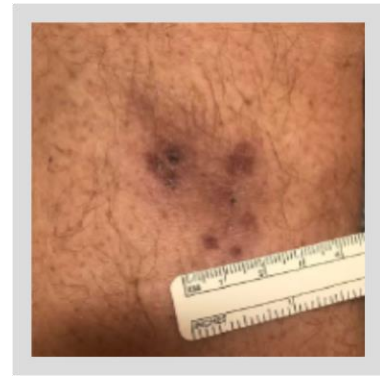
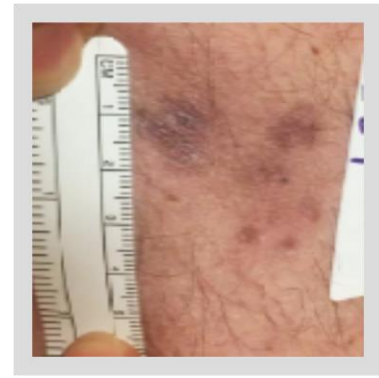
Example of response: Patient with CR

Tumor stage at enrollment: **IIIb**
T4a, N2b, M0

RECIST 1.1: CR

Prior therapies: Surgery
Ipilimumab
Dabrafenib + Trametinib
Pembrolizumab

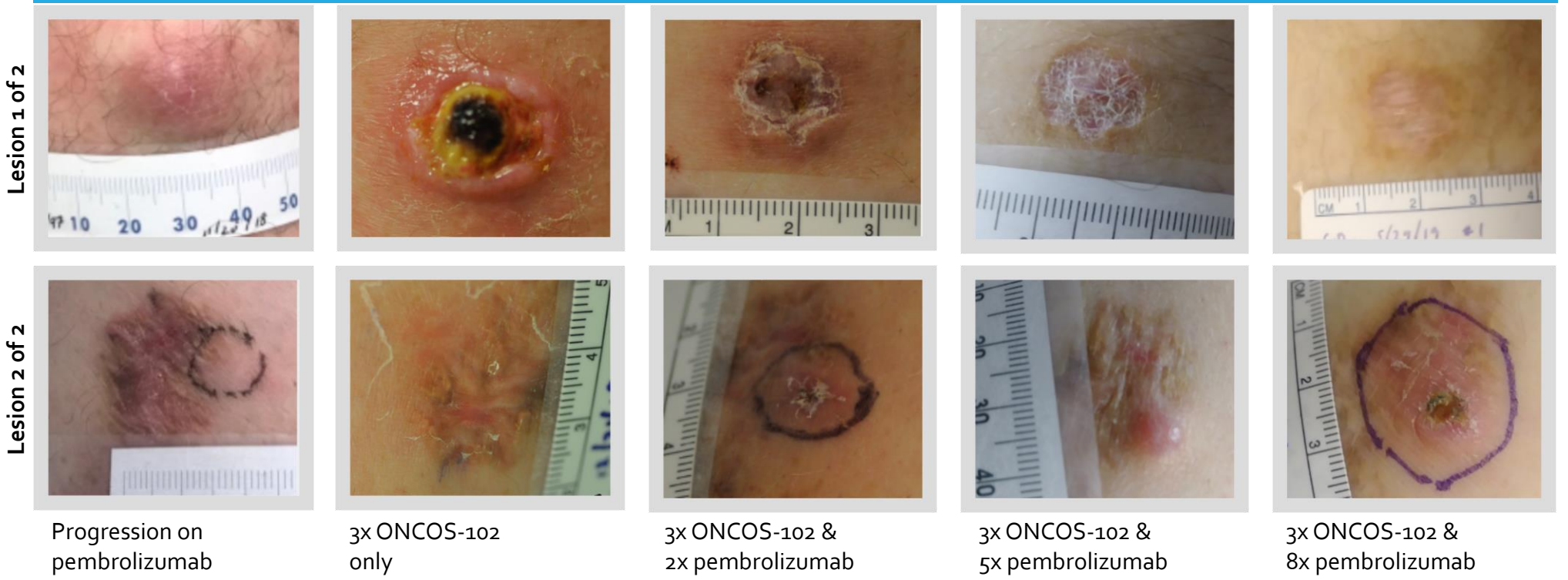
Target lesion 1 of 1

Baseline	**Week 3**	**Week 9**	**Week 18**	**Week 27 (EoS)**
				
Progression on pembrolizumab	3x ONCOS-102	3x ONCOS-102 & 2x pembrolizumab	3x ONCOS-102 & 5x pembrolizumab	3x ONCOS-102 & 8x pembrolizumab

Preliminary data

Example of response: Patient with PR

Tumor response, 2 of 2 injected lesions



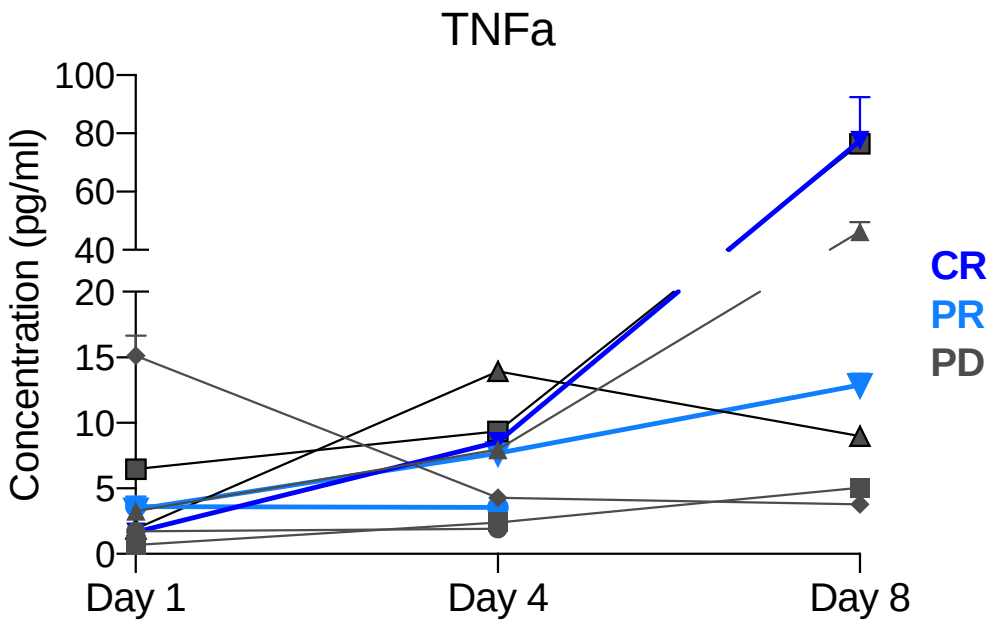
Progression on pembrolizumab	3x ONCOS-102 only	3x ONCOS-102 & 2x pembrolizumab	3x ONCOS-102 & 5x pembrolizumab	3x ONCOS-102 & 8x pembrolizumab

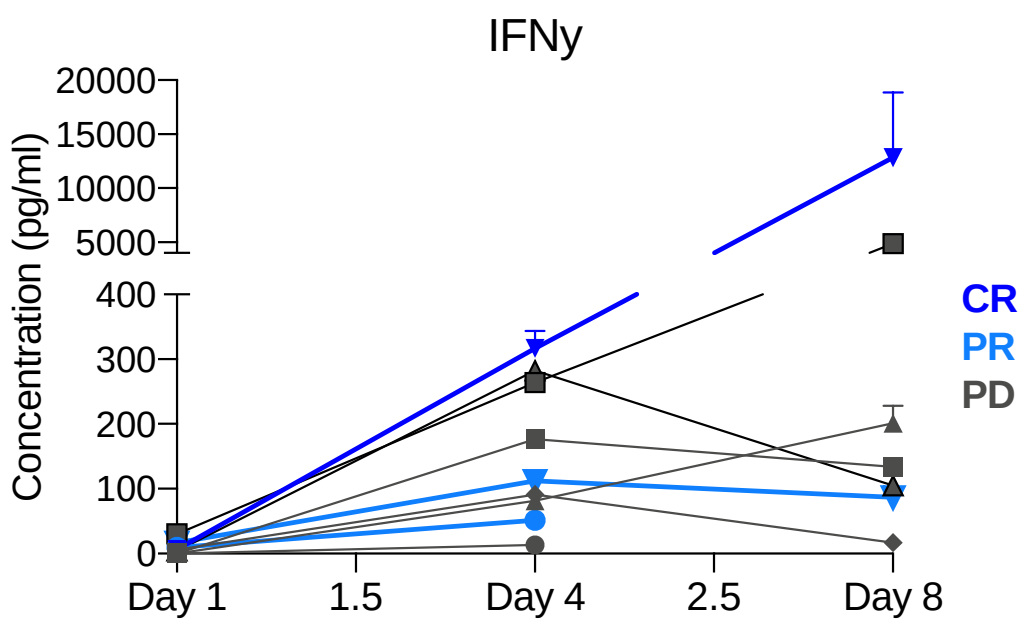
Patient characteristics

Tumor stage at enrolment:	**IV** T4a, N1b, M1	**Prior therapies:**	Surgery Talimogene-laherparepvec (T-vec) Ipilimumab Pembrolizumab
RECIST 1.1:	**PR,** week 9-27		

Upregulation of proinflammatory cytokines in all patients

Systemic expression of proinflammatory cytokines

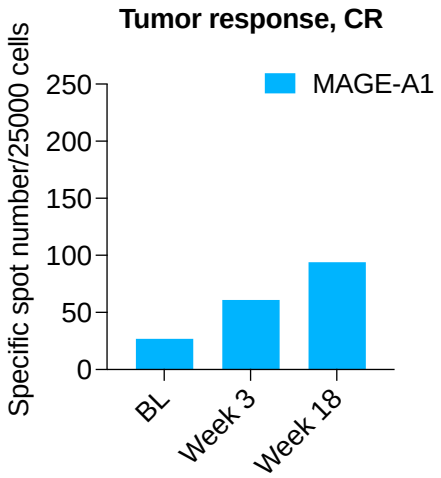


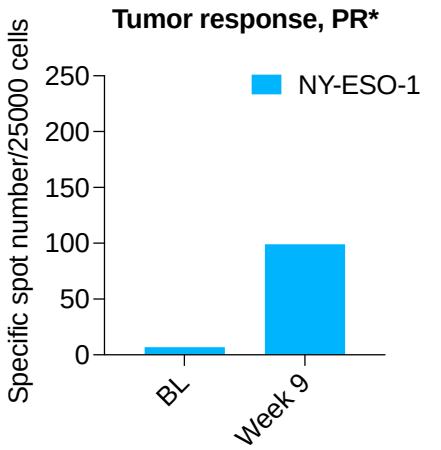


Preliminary data

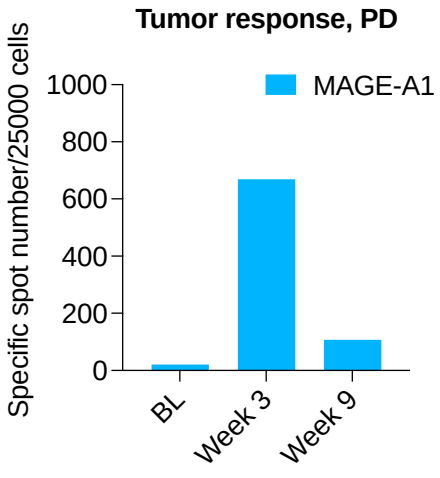
Systemic increase in tumor targeting T-Cells

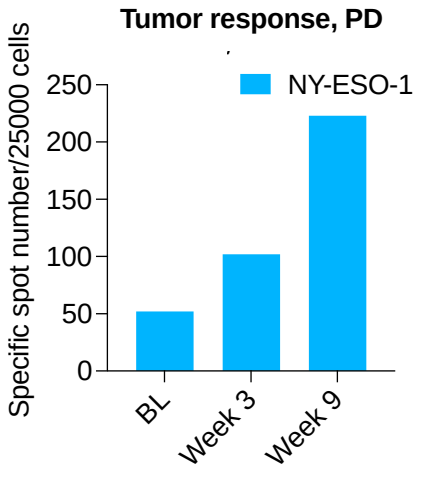
IFNγ ELISPOT, spot number/25,000 cells





* Week 3 analysis not performed

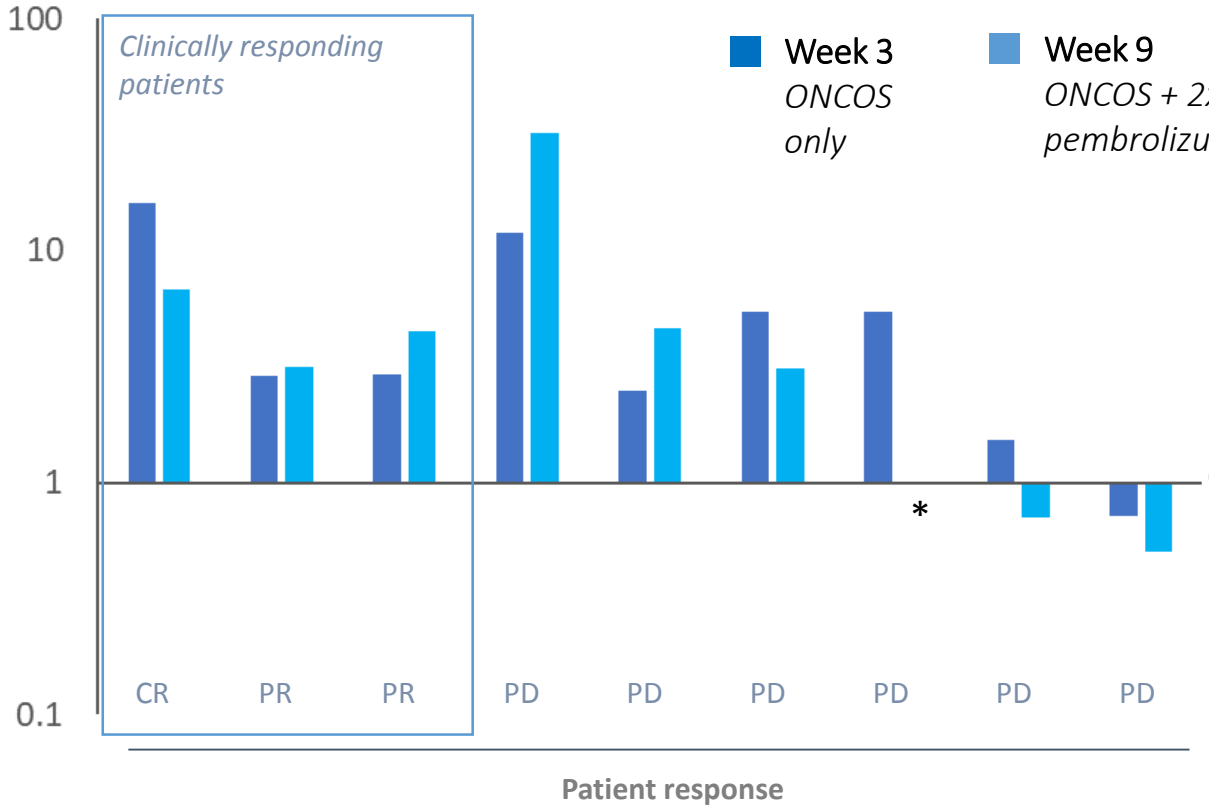




Preliminary data

Increased T-cell infiltration in ONCOS-102 injected tumors is necessary but not sufficient for response

CD8+ T-cell tumor infiltration, -fold change from baseline



All 9 patients had low or very low CD8+ T-cell infiltration at baseline

* Week 9 analysis not available

CR= Complete Response, PR= Partial Response, PD: Progressive Disease

Preliminary data

Conclusions

Sequential ONCOS-102 and pembrolizumab treatment in advanced anti-PD-1 refractory melanoma patients showed:

- Acceptable safety profile; most common ONCOS-102 related adverse events were fevers, chills, and myalgias
- ORR: 3 of 9 patients (RECIST 1.1)
- Upregulation of proinflammatory cytokines
- Systemic development of anti-tumor immune responses
- Increased infiltration of CD8+ T cells in ONCOS-102 injected tumors

Part 2 of this pilot study is currently enrolling an additional 12 patients to receive 12 injections of ONCOS-102 with pembrolizumab

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Petr Hausner
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Targovax

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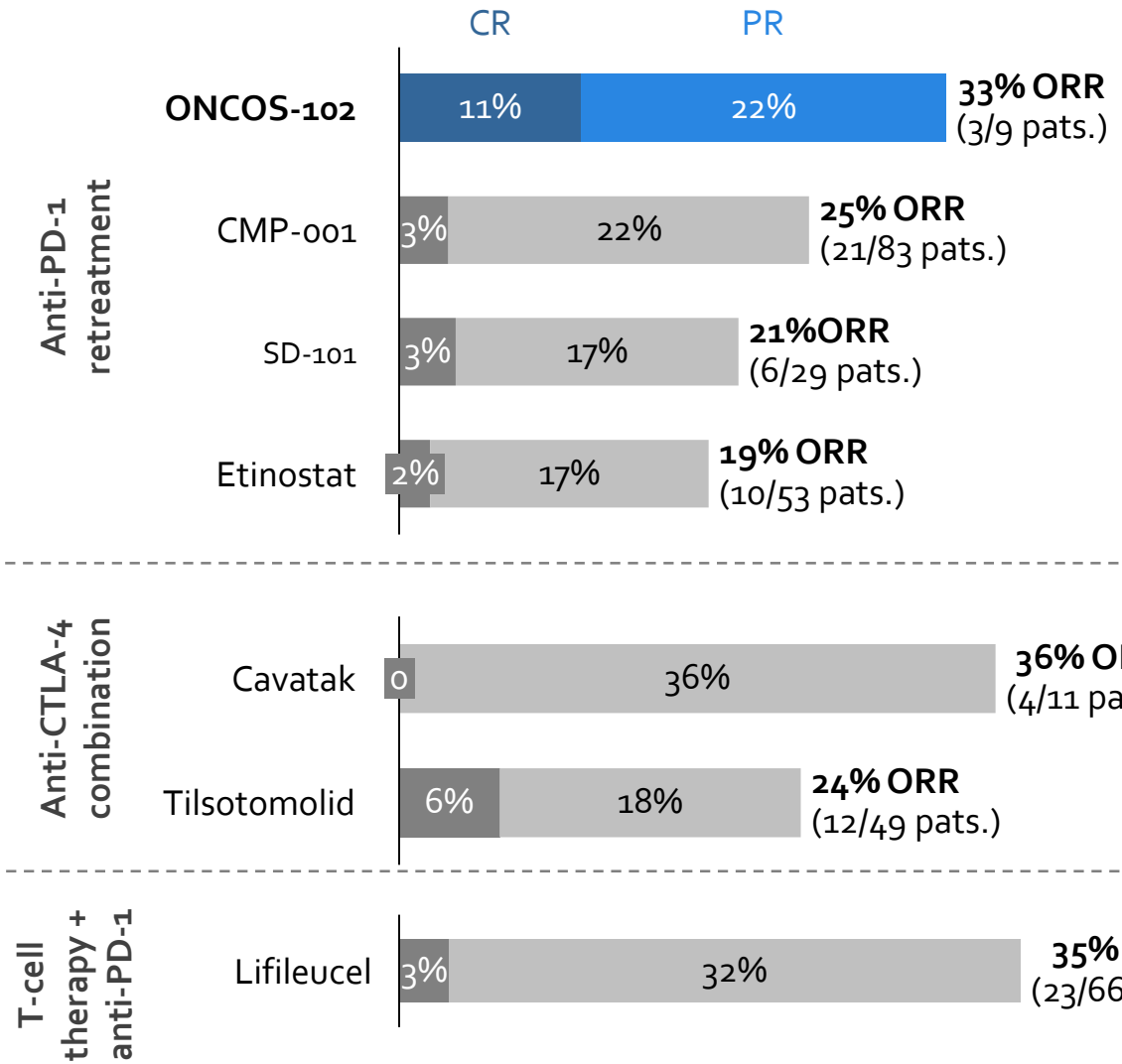
Trine Jensen Gjertsen

ONCOS-102 + Keytruda data in context of published anti-PD-1 refractory melanoma data



Comment

- *Part 1 with three injections only*
- *Checkmate Pharma, TLR-9 agonist*
- *Data from high dose cohort*
- *Dynavax, TLR-9 agonist*
- *Syndax Pharma, HDAC inhibitor*

Most pats CTLA4 naïve, 10-20% ORR expected

- *Merck (Viralytics), Oncolytic virus, up to 20 injections*
- *Idera, TLR-9 agonist*
- *IOvance, autologous TIL therapy with IL-2*
- *Complex and expensive manufacturing*

Trials and combinations to watch in melanoma

	Example compounds	Trials to watch
Novel immune checkpoint inhibitors	LAG-3, TIM-3, TIGIT	• LAG-3 relatimab in combination with Nivolumab in stage IV IO naïve melanoma • TIM-3 mono and in combination with anti-PD-1 in IO pretreated stage IV melanoma
Oncolytic viruses	T-VEC, Cavatak, ONCOS-102	• T-VEC phase III 1L combination with Keytruda (Masterkey-265) • Cavatak phase II 1L combination with Keytruda • ONCOS-102 phase I in PD-1 refractory in combination with Keytruda
Immune stimulatory agents	TLR9, CD40, OX40, IL-2	• CMP-001 in PD-1 refractory, phase II combination with Keytruda • Tilsotolimod in PD-1 refractory, phase III combination with Yervoy • Bempegaldesleukin + nivolumab in 1L, phase III (CA045-001)
Adoptive T-cell therapy	Lifileucel	• TIL therapy PD-1 refractory, pivotal phase II trial in combination with IL-2
BRAFi/MEKi	Mekinist, Tafinlar	• MEKi/BRAFi in combination with pembrolizumab in 1L BRAF V600E melanoma

So…what's next in melanoma?

- Frontline trials
- Post PD-1 trials
- Neoadjuvant Approaches
- Melanoma as a crystal ball for "IO"
  - Newest ideas
  - Benchmarks
  - Highest unmet need

Frontline Trials in Melanoma: Big Ones

- Randomized, PD-1 +/- XYZ
  - **LAG-3**: Nivolumab +/- Relatlimab (NCT03470922)
  - **T-VEC**: Pembrolizumab +/- TVEC (NCT02263508)
  - **IL-2 directed**: Nivolumab +/- BEMPEG (NCT03635983)
  - VEGF: Pembrolizumab +/- Lenvatinib (NCT03820986)

- BRAF-MEK +/- PD-1: Enco-Bini-Spartalizumab (NCT02967692)

Frontline Trials in Melanoma: Big Ones

- Large trials, 500-700+ patients
- What do we need for a new standard?
  - **OS, not just PFS and ORR**
  - Tolerability
  - Schedule / ease of use
- We are a few years away from making a new frontline standard
- Existing frontline treatment is tolerable, relatively easy, and can be durable

Post PD-1 Trials: Trends

- Critical need to develop new treatments, but it's getting harder to do it well

- Rigidly defining "PD-1 resistance"
- Slowly relaxing prior toxicity requirements (…too slowly)
- Highly selective trials (e.g. lifileucel)
- The specter of ipilimumab: 20% ORR, durability
- Single arm ORR or Randomized Trials

Neoadjuvant Trials: Pros and Cons

Pros

- Faster readout than frontline
- Easy access to tissue for mechanistic and biomarker studies
- Patients (usually) like these, as long as there is no placebo
- FDA appears more willing than before to consider "major response" clinically meaningful

Cons

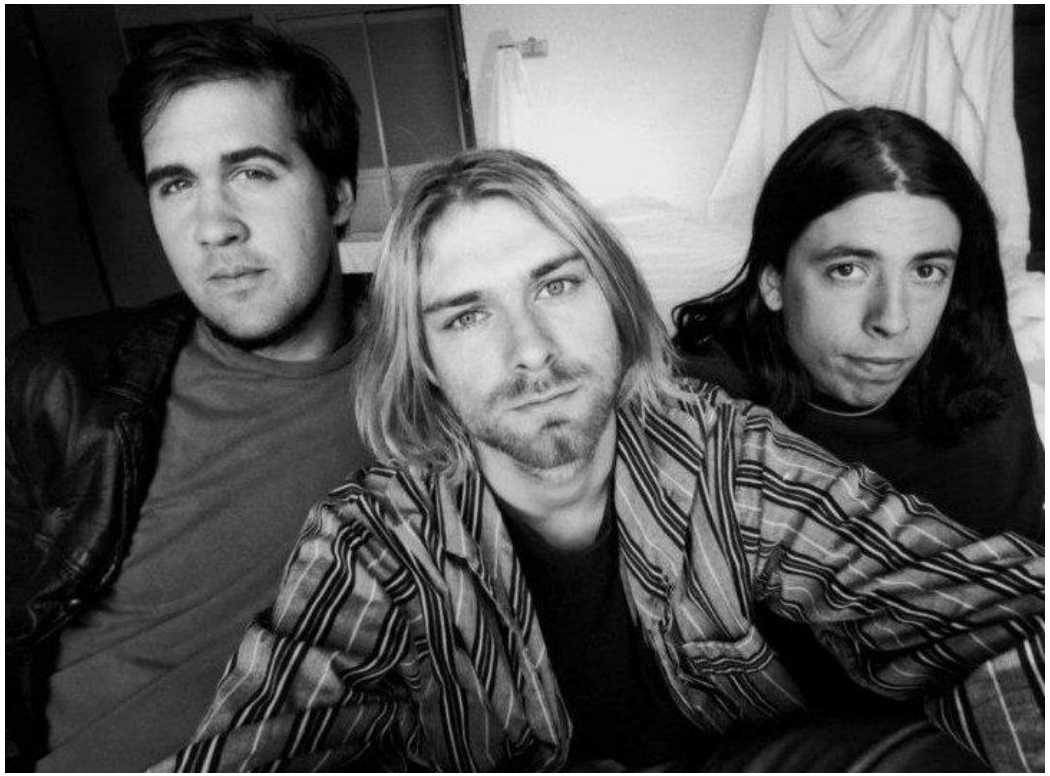
- A relative minority of cutaneous melanoma presents with bulky stage 3 disease
- Path CR is still a relative leap of faith
- Physicians are already doing this with nivo 3 + ipi 1

Neoadjuvant Trials: Selected Candidates

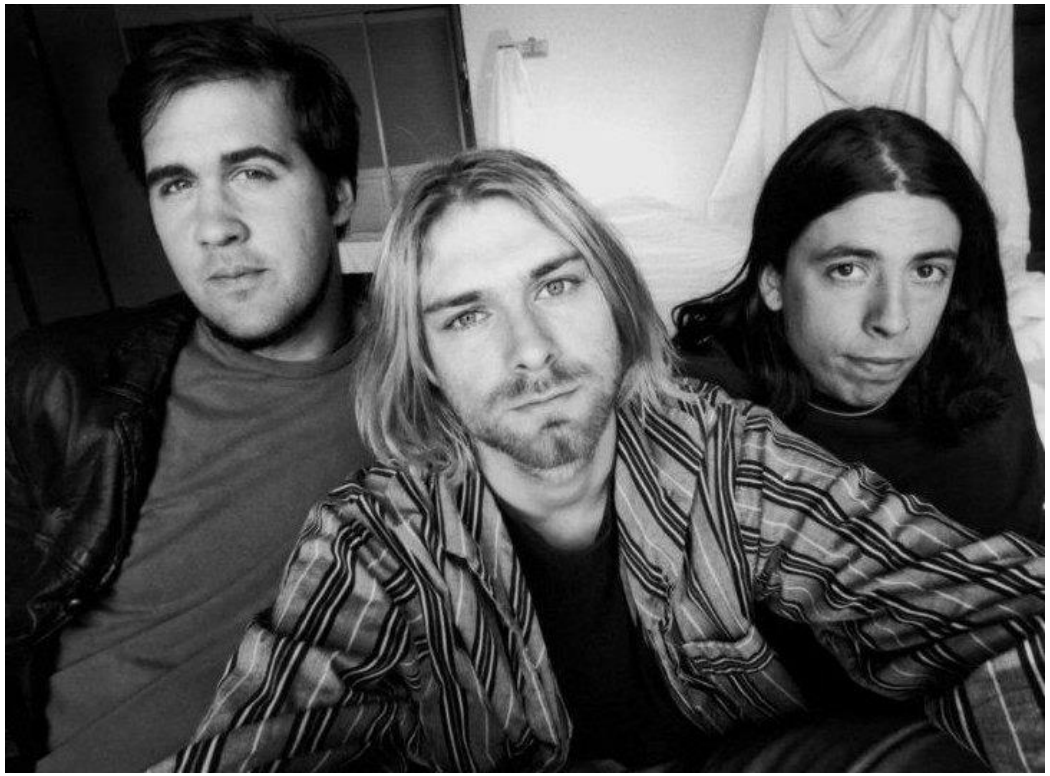
- All with PD-1 backbone

- BRAF-MEK
- Checkpoint combinations: CTLA-4, LAG-3
- Oncolytic Viruses: e.g. T-VEC, CAVATAC
- TLR9 Agonists: e.g. CMP-001

Melanoma: Small Histology, but Influential



Melanoma: Small Histology, but Influential



The Pixies

(Melanoma)

Nirvana

(NSCLC, breast)

Melanoma: Small Histology, but Influential

- We usually set trends followed by the bigger histologies

- Easily accessible tissue
- Relatively aggressive disease
- Hot (cutaneous) vs cold (uveal) vs mixed (mucosal) models
- Patient buy-in for biomarker heavy trials

What's Next? Other Approaches

- Microbiome manipulation (e.g. Seres-401)
- CD3 fusion protein constructs (e.g. tebentafusp against gp100)
- Personalized neoantigen platforms
- CAR-T baskets
- Uncoupling toxicity from efficacy: TNF antagonist co-administration

What's Next? Highest Unmet Needs

- Uveal melanoma
  - No frontline standard option
  - Tebentafusp registration trial(s), but HLA-A restricted
- PD-1 Refractory Cutaneous Melanoma
  - Enriched for NRAS mutant biology
  - If any prior tox, subsequent trials are limited

- Leptomeningeal Disease / active brain mets

What Should Benchmarks be?

- Well defined "PD-1 resistant" definition
- Study that CONSORT diagram!
  - Screen failures?
  - Time to fully accrue?
- ORR and PFS only in select settings
  - Uveal melanoma responses are probably real successes
  - 2nd line cutaneous melanoma responses may not be
- Randomization, OS are still gold standards

Thanks!