Memorial Sloan Kettering Cancer Center™

Melanoma and oncolytic adenoviruses

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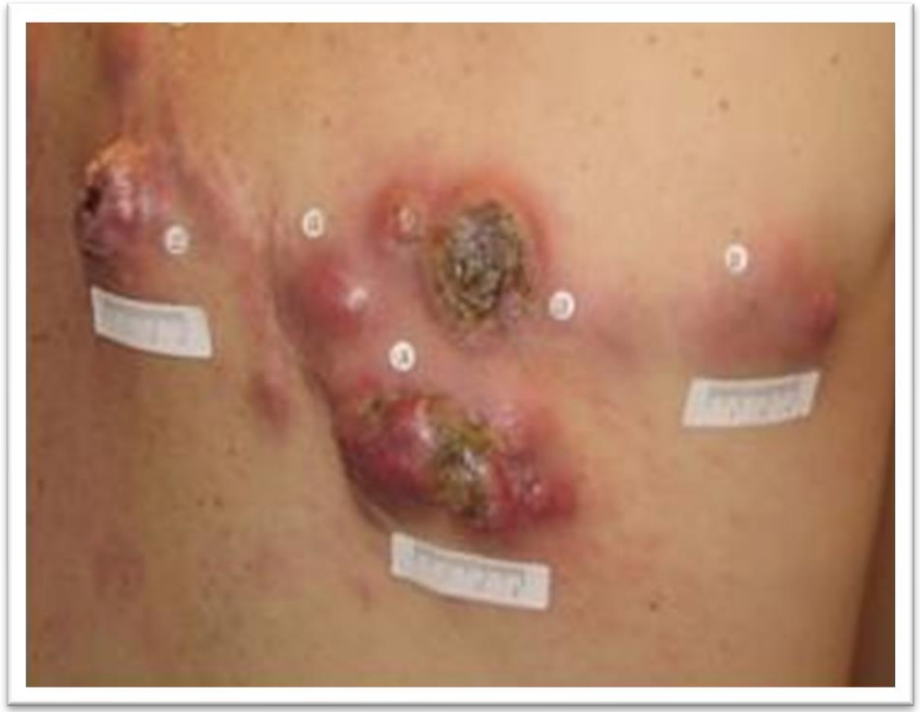
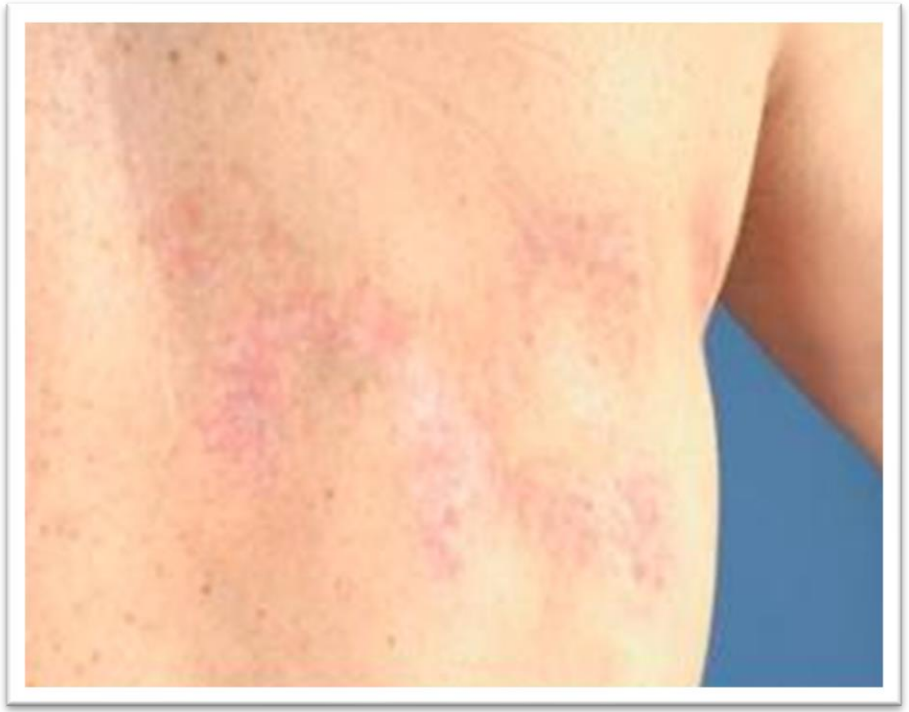
Immunotherapy has revolutionized the treatment of malignant melanoma

Real world example – Patient in an ipilimumab checkpoint inhibitor trial



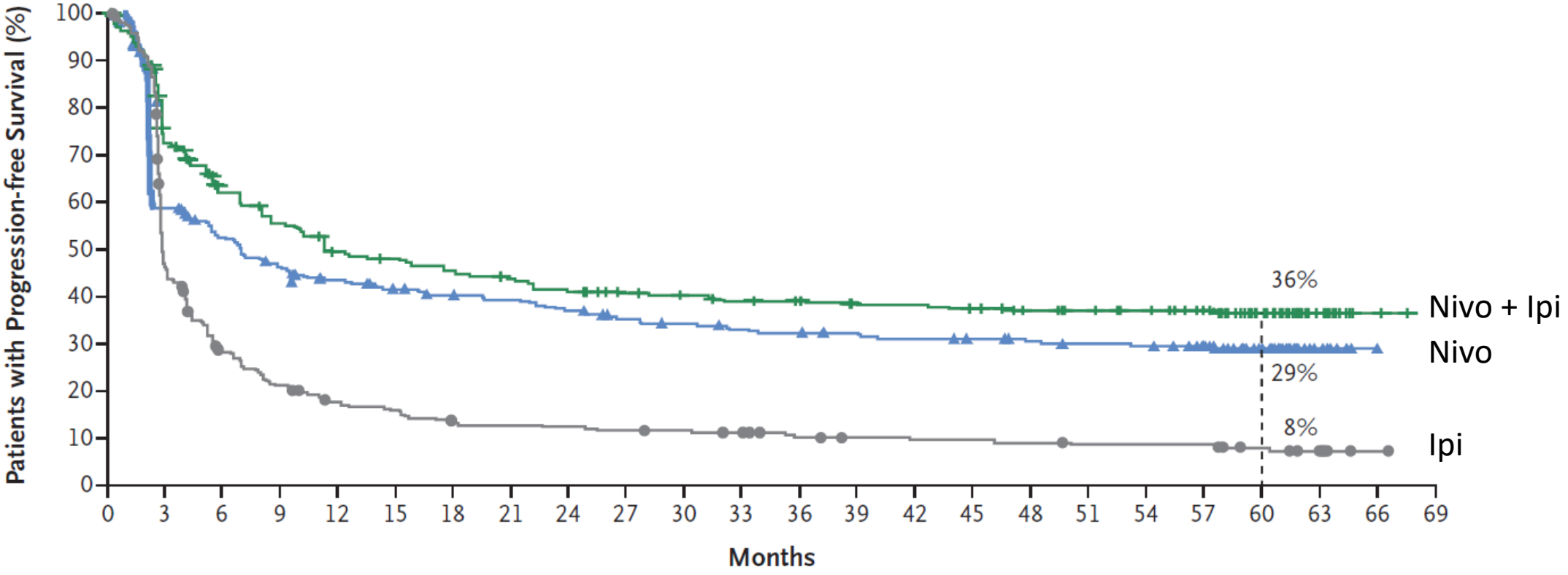
Prior to starting ipilimumab



One year of ipilimumab treatment

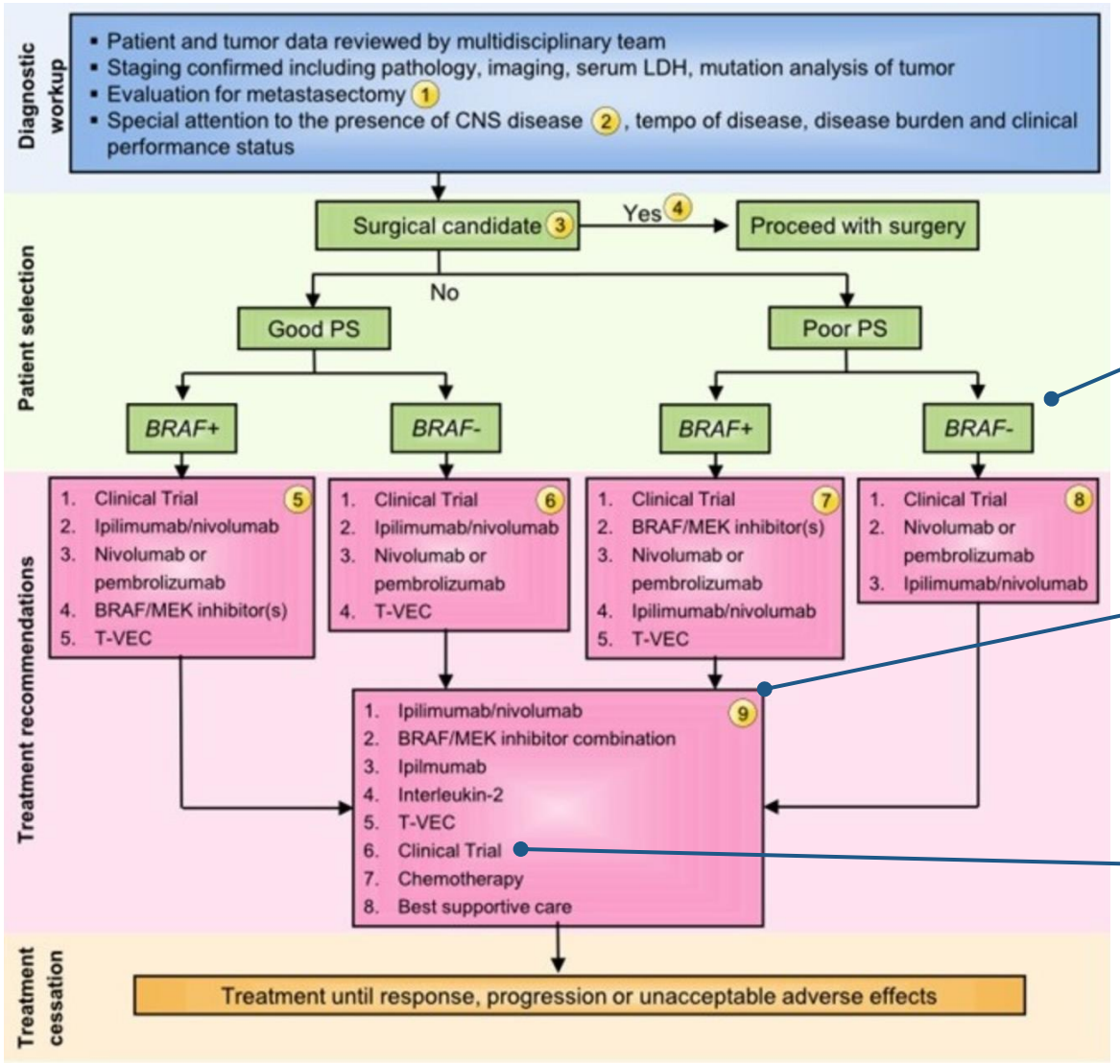
Photo courtesy Jedd Wolchok

PD-1 blockade has surpassed CTLA-4, and become the cornerstone of melanoma treatment



Source: Larkin et al, NEJM 2019

SITC treatment algorithm for late stage melanoma



Checkpoint inhibitors and BRAFi/MEKi are the mainstay frontline therapy in unresectable melanoma

Few alternatives exist following progression on CPI and/or BRAFi/MEKi

Treatment resistance – option of clinical trial or best supportive care

SOURCE: Society for Immunotherapy of Cancer (SITC)

PD-1 checkpoints are effective 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

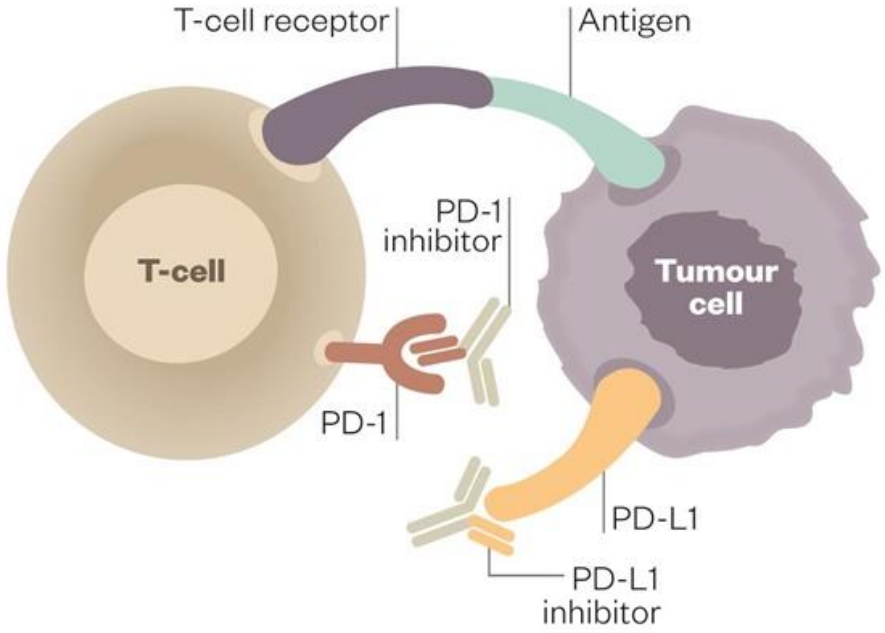
- Responses can last for years, but not forever

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

- PD1 monotherapy: 1 in 4 require steroids
- PD1 + CTLA4 combination: 3 in 4 require steroids



Graphic: DelveInsight

Post PD-1/CTLA4/BRAF-MEKi progression, only experimental and off-label options are available

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

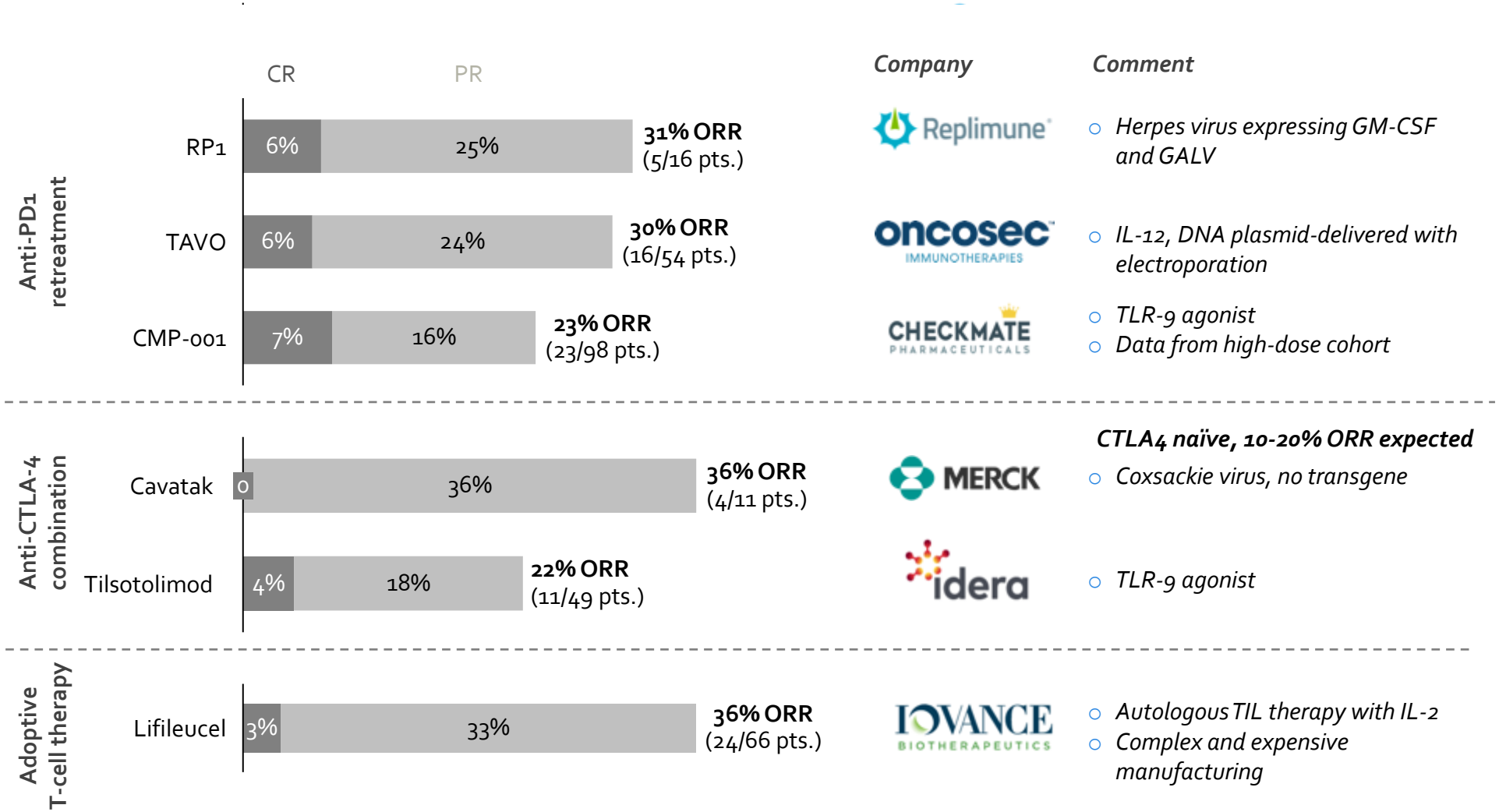
Clinical Trials (selected)

- PD-1 combination with:
  - Oncolytic virus
  - TLR9 agonist
  - LAG-3 inhibitor
  - Cytokines (IL-2, IL-12)
  - Neoantigen vaccines
  - TCR bispecifics
- Tumor Infiltrating Lymphocyte (TIL) trials

Off-label uses

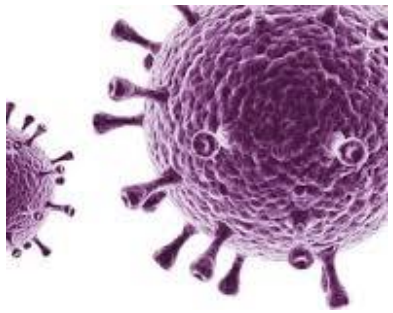
- BRAF + MEK + PD-1
- T-VEC + PD-1 inhibitor
- Radiation + PD-1 +/- Ipilimumab

Response rates reported from PD-1 checkpoint inhibitor refractory melanoma clinical trials



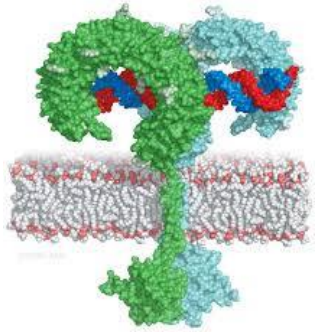
Targovax market analysis, January 2021.

Promising experimental therapies available for PD-1 resistant patients



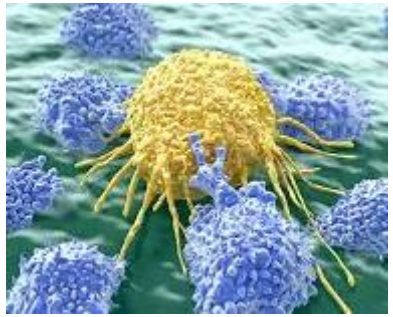
Oncolytic viruses

- Trigger oncolysis and inflammatory response via TLR-9 and other
- Reverses local immuno-suppression
- Trials ongoing in combination with PD-1 and CTLA-4



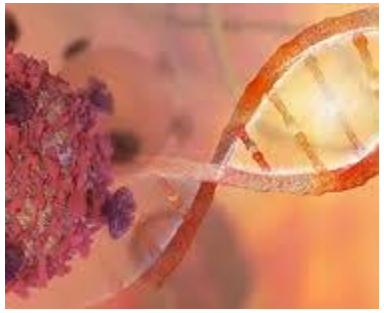
TLR-9 agonists

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



TIL therapy

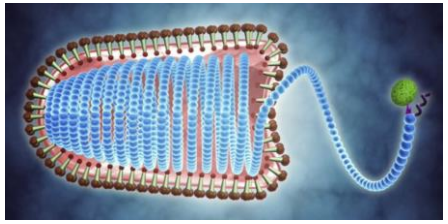
- Autologous T-cells harvested from the patient's tumor
- Combination trials ongoing with systemic immune activators (eg IL-2)
- Potentially efficacious, but significant cost and logistics hurdles

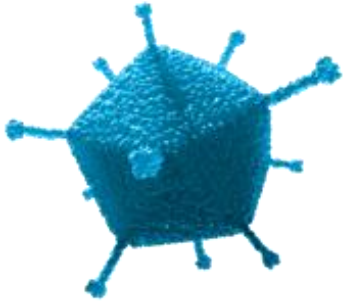


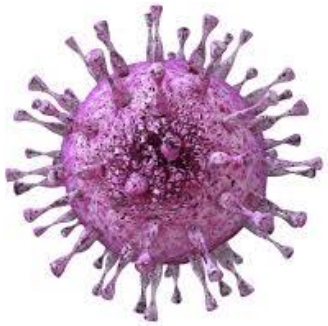
Neoantigen vaccines and TCRs

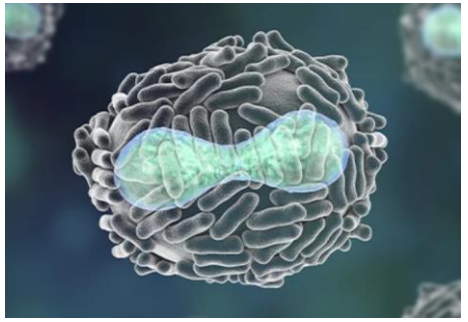
- Trigger T-cell responses to shared or personalized neoantigens
- Either personalized vaccines or shared tumor antigen approaches
- Trials ongoing with PD-1

Overview of the most common oncolytic virus classes





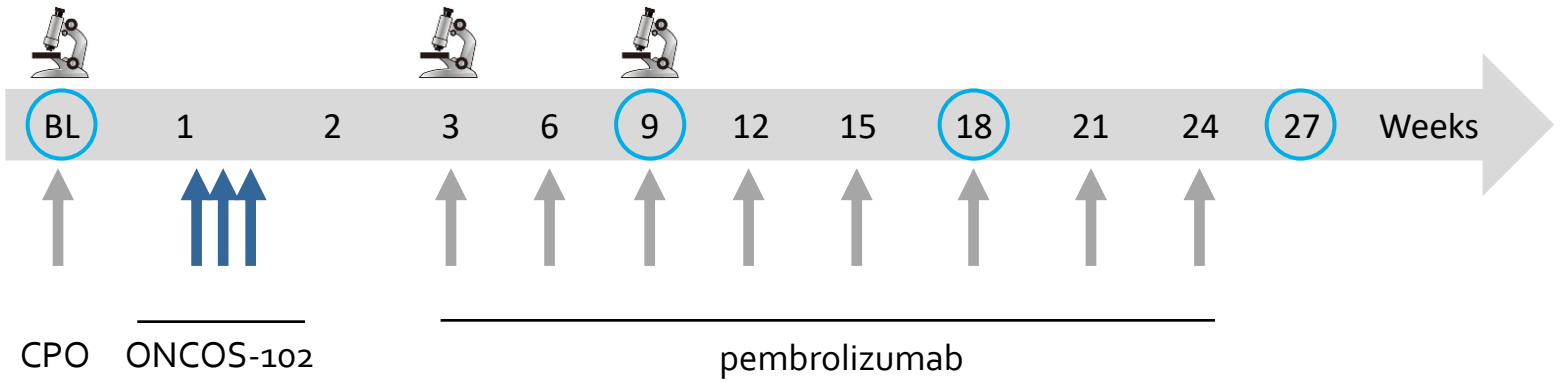




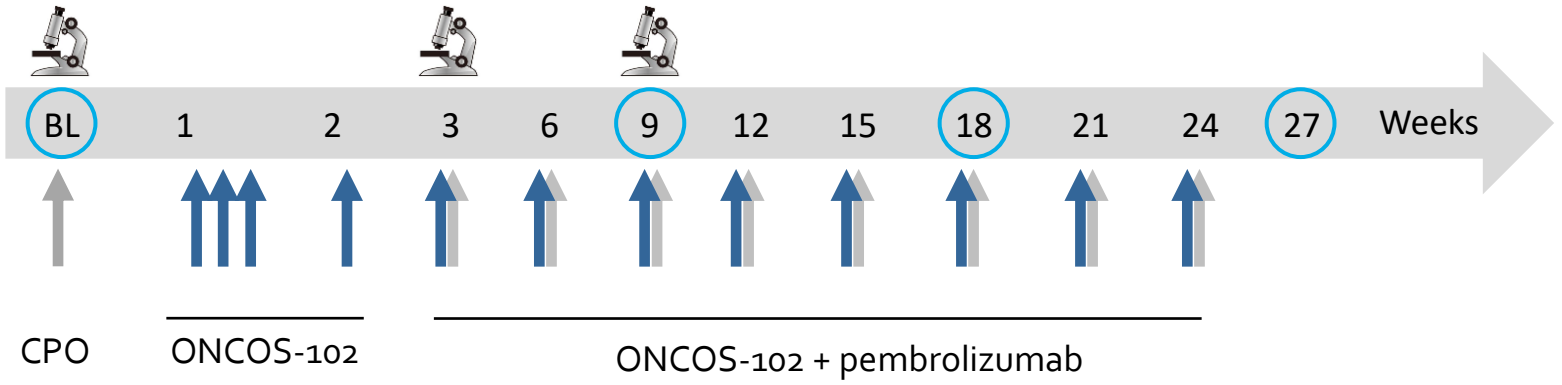
	Small RNA viruses	Adenovirus	Herpes viruses	Vaccinia virus
⊕	○ **Highly oncolytic** ○ **Highly inflammatory**	○ **Highly inflammatory** ○ **Versatile** DNA backbone	○ **Large payload** capacity ○ **Only approved** virus class	○ **Large payload** capacity ○ Used as vector for first, historic vaccines
⊖	○ **Limited payload** capacity ○ Poor stability	○ Less payload capacity than Herpes / Vaccinia	○ **Low immunogenicity** ○ Latent infection cycle	○ **Low immunogenicity** ○ Large size, high complexity
📊	○ Only **sporadic evidence** of clinical efficacy	○ Several candidates with **promising early data** ○ Vector for several **effective COVID-19 vaccines**	○ **Mixed recent data** ○ Imlygic **commercial failure**	○ Several recent **negative clinical trials**

Study design of ONCOS-102 phase I trial in PD1 checkpoint-refractory melanoma

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



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



Imaging

Biopsy

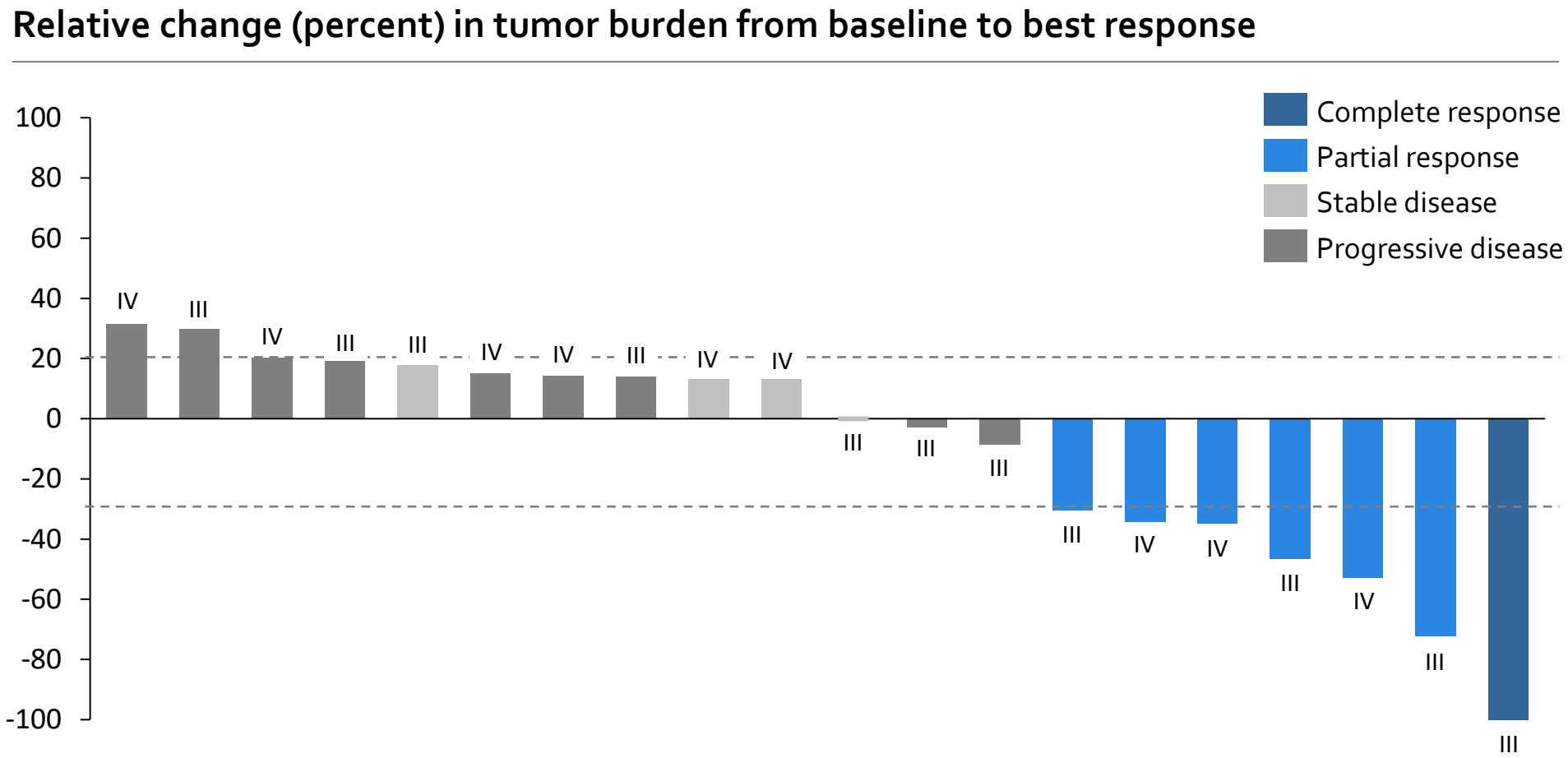
CPO: Cyclophosphamide

Patient and disease characteristics

Parameters	Part 1 (n=8)	Part 2 (n=12)	Total (N=20)
Age (median)	70.5y	72y	72y
Time from diagnosis to start of ONCOS-102 (median)	6.9y	2.9y	4.5y
Number of treatments prior to study (average) - Surgery (average) - Treatments ex. surgery (average)	5.3 2.1 3.1	5.9 1.9 3.9	5.6 2.0 3.6
Time (months) from last anti-PD1 to study start (median)	1.8m	1.9m	1.9m
Number of prior checkpoint treatment regimens (average)	1.8	2.3	2.2
Prior CTLA-4 treatment (number of patients, %)	4 (50%)	8 (67%)	12 (60%)
Baseline number of lesions (median)	4.0	8.5	7.0
Baseline tumor burden RECIST1.1 (mm, median)	37.5	73.5	55.0
Tumor stage at enrollment - Stage III - Stage IV	 6 2	 5 7	 11 9

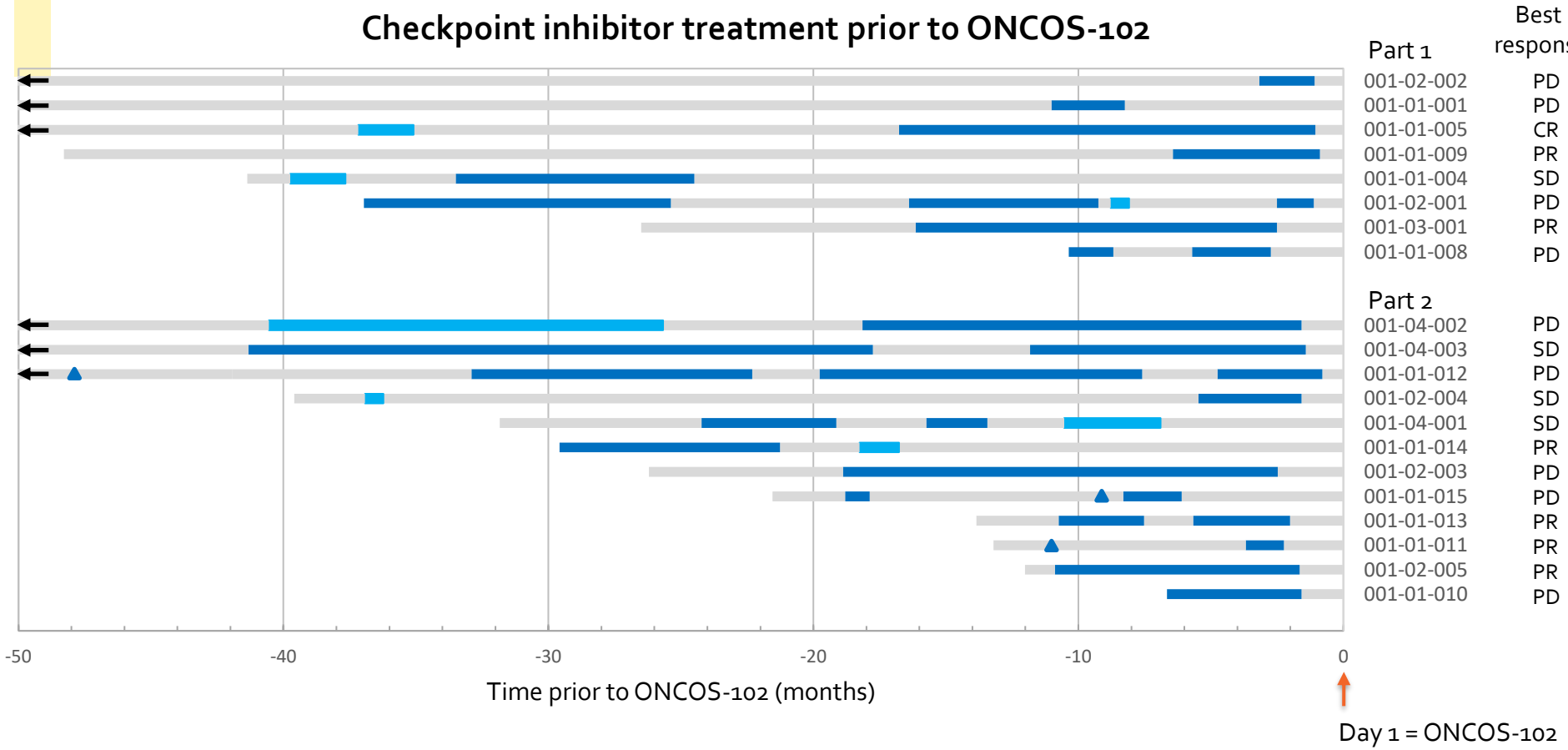
More advanced disease in Part 2

Objective responses observed in 7 out of 20 patients (35% ORR)



Stage at enrollment
Response evaluated by RECIST 1.1 in at least one CT scan

6 of 7 responders had last aPD1 treatment less than 3 months prior to entering the trial



CPI treatment prior to trial inclusion:

15 / 20 patients last aPD1 treatment < 3 months (6 / 7 PR/CR)

3 / 20 patients last aPD1 treatment > 6 months (no PR)

2 / 20 patients last treatment aCTLA4 monotherapy > 6 months (1 / 7 PR)

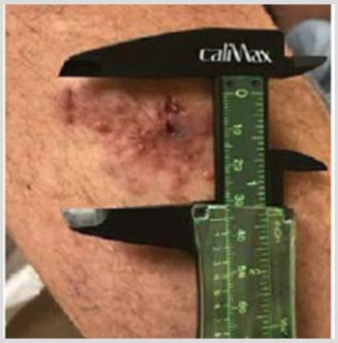
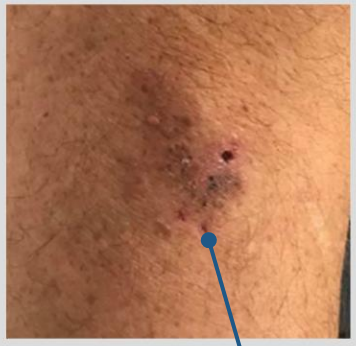
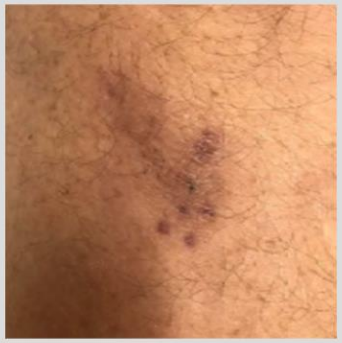
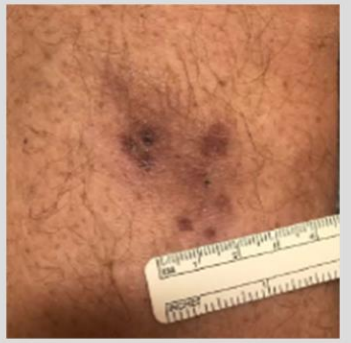
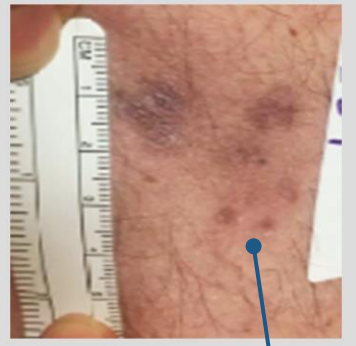
Case example 1 – patient with complete response

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

RECIST 1.1: CR

Prior therapies:
Surgery
Radiation
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

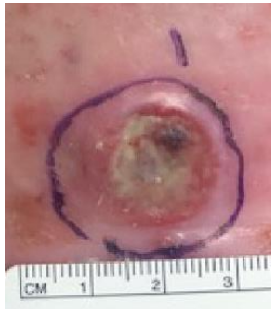
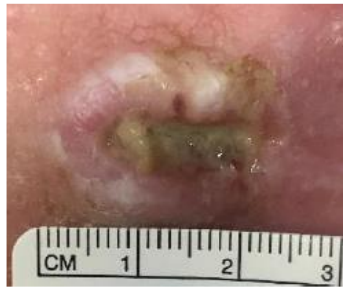
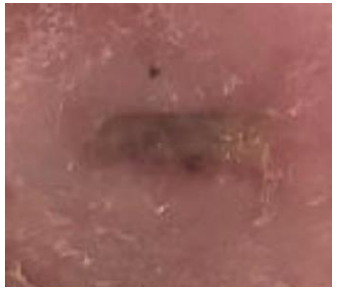
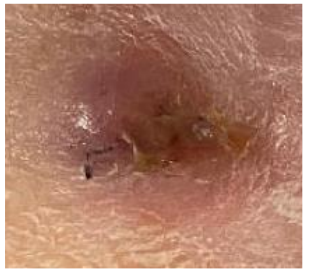
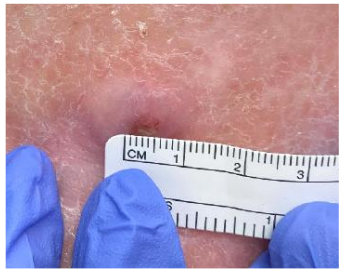
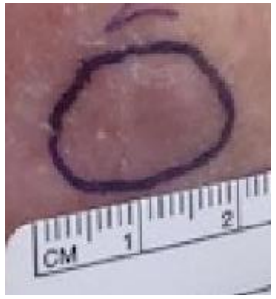
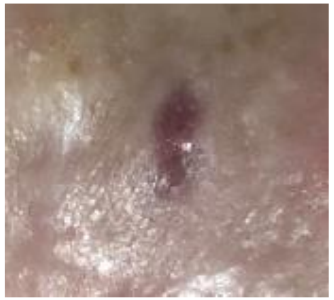
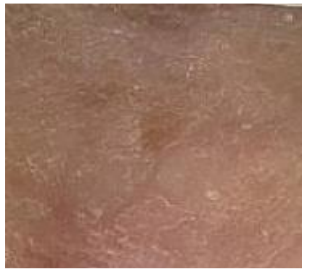
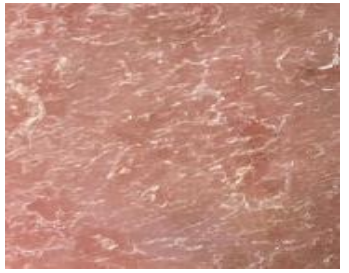
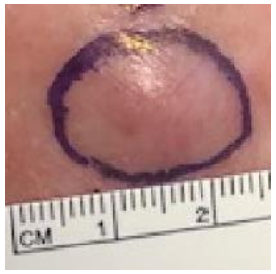
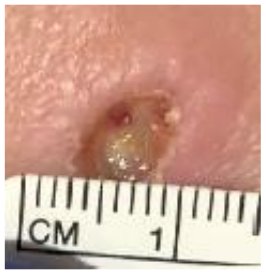
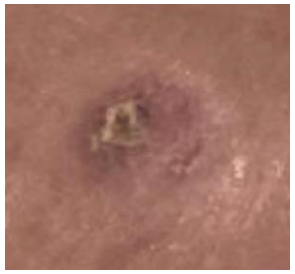
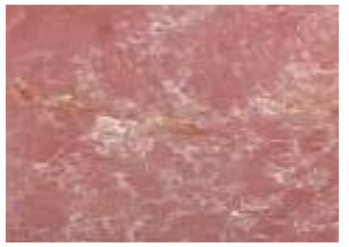
Tumor regression following ONCOS-102 only priming phase

Discoloring and scar tissue from injections and biopsies

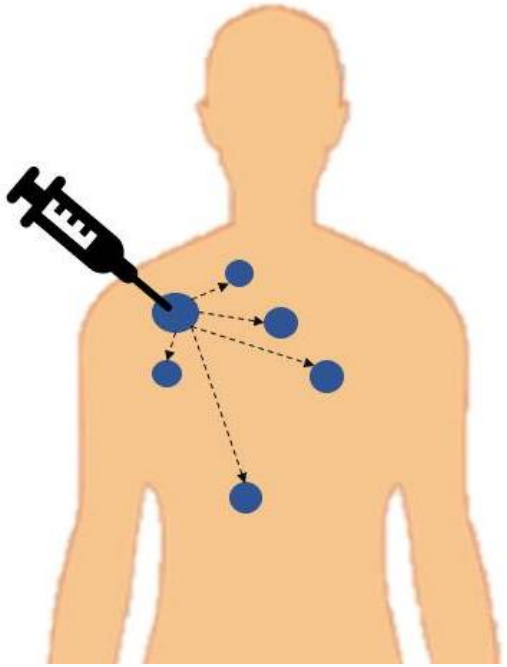
Case example 2 - Patient with PR following 2 separate lines of prior PD-1 blockade

- Stage IIIC at enrollment, 7 lesions in total
- 3 non-target lesions injected
- Prior therapies:
  - Surgery
  - Nivolumab x 2
- Last aPD1 treatment 2 months before ONCOS-102
- PR Week 9-27 by RECIST 1.1, no target lesions injected
- Complete regression in non-injected lesion

Tumor images, 3 of 3 injected lesions

	Baseline	*Week 3*	*Week 9*	*Week 18*	*Week 27 (EoS)*
Lesion 1 of 3					
Lesion 2 of 3					
Lesion 3 of 3					
	Progression on nivolumab	4x ONCOS-102 only	6x ONCOS-102 & 1x pembrolizumab	8x ONCOS-102 & 2x pembrolizumab	11x ONCOS-102 & 4x pembrolizumab

Evidence of systemic (abscopal) effect – responses observed in several non-injected lesions



Conservative definition of abscopal effect per lesion:

- ≥30% tumor reduction from baseline
- ≥ 5mm absolute reduction

Abscopal effect observed in 4 / 20 patients (20%)

- 1 / 8 patients in Part 1 (12.5%)
- 3 / 12 patients in Part 2 (25%)

Complete regression (100%) of a non-injected lesion observed in two patients

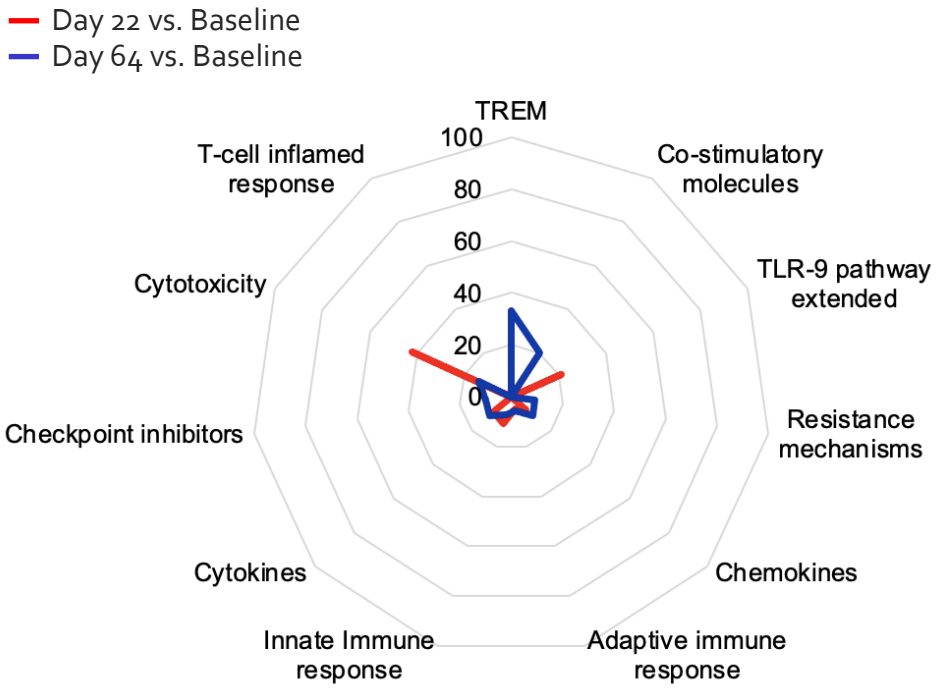
ONCOS-102 and the combination with pembrolizumab is safe and well tolerated

Adverse Event, Preferred term	Subjects, n	Events, n	Grade 1 / 2 events	Grade 3	Grade 4
AEs related to ONCOS-102 +/- CPO					
Pyrexia	10	24	24	-	-
Chills	9	23	23	-	-
Nausea	6	10	10	-	-
Injection site pain	4	6	6	-	-
Myalgia	3	6	6	-	-
Rash maculo-papular	4	5	5	-	-
Fatigue	5	5	5	-	-
Vomiting	4	4	4	-	-
Diarrhoea	3	4	4	-	-
Injection site reaction	3	3	3	-	-
Alanine aminotransferase increased	2	2	2	-	-
Hypotension	2	2	2	-	-
Pruritus	2	2	2	-	-
Large intestine infection	1	1	-	1	-
AEs related to ONCOS-102 + pembrolizumab +/- CPO					
Aspartate aminotransferase increased	2	4	4	-	-
Pyrexia	3	3	3	-	-
Alanine aminotransferase increased	1	3	3	-	-
Blood alkaline phosphatase increased	1	2	2	-	-
Diabetic ketoacidosis	1	1	-	-	1
Type 1 diabetes mellitus	1	1	-	-	1

For Grade 1 and 2 adverse events only 2 events and more are listed. No Grade 5 events occurred

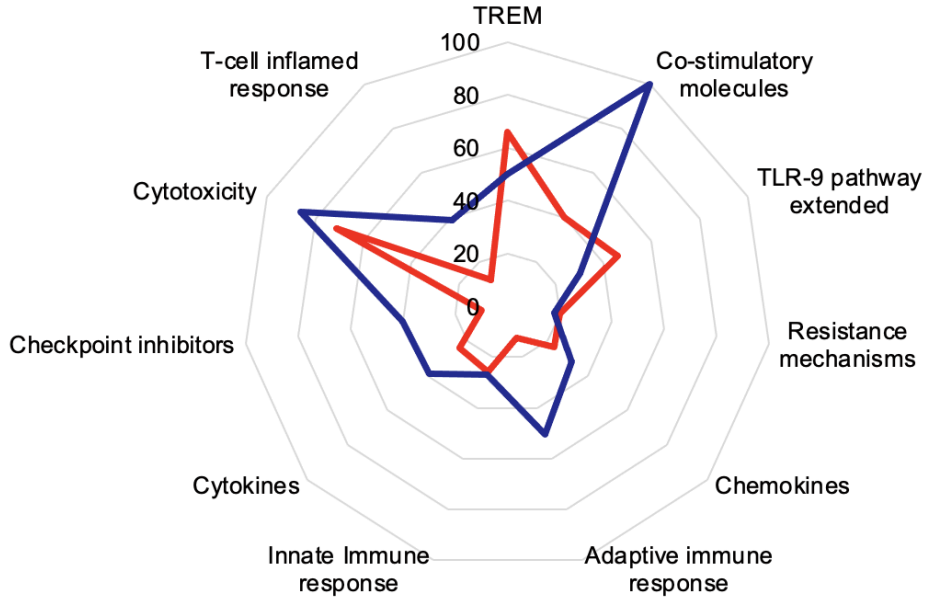
Broad and persistent modulation of immune-related gene expression observed in Part 2 of the trial

Modulation of gene expression following ONCOS-102 treatment; % modulated genes



Part 1

Day 22 & Day 64 (n=2)
Baseline (n=6)

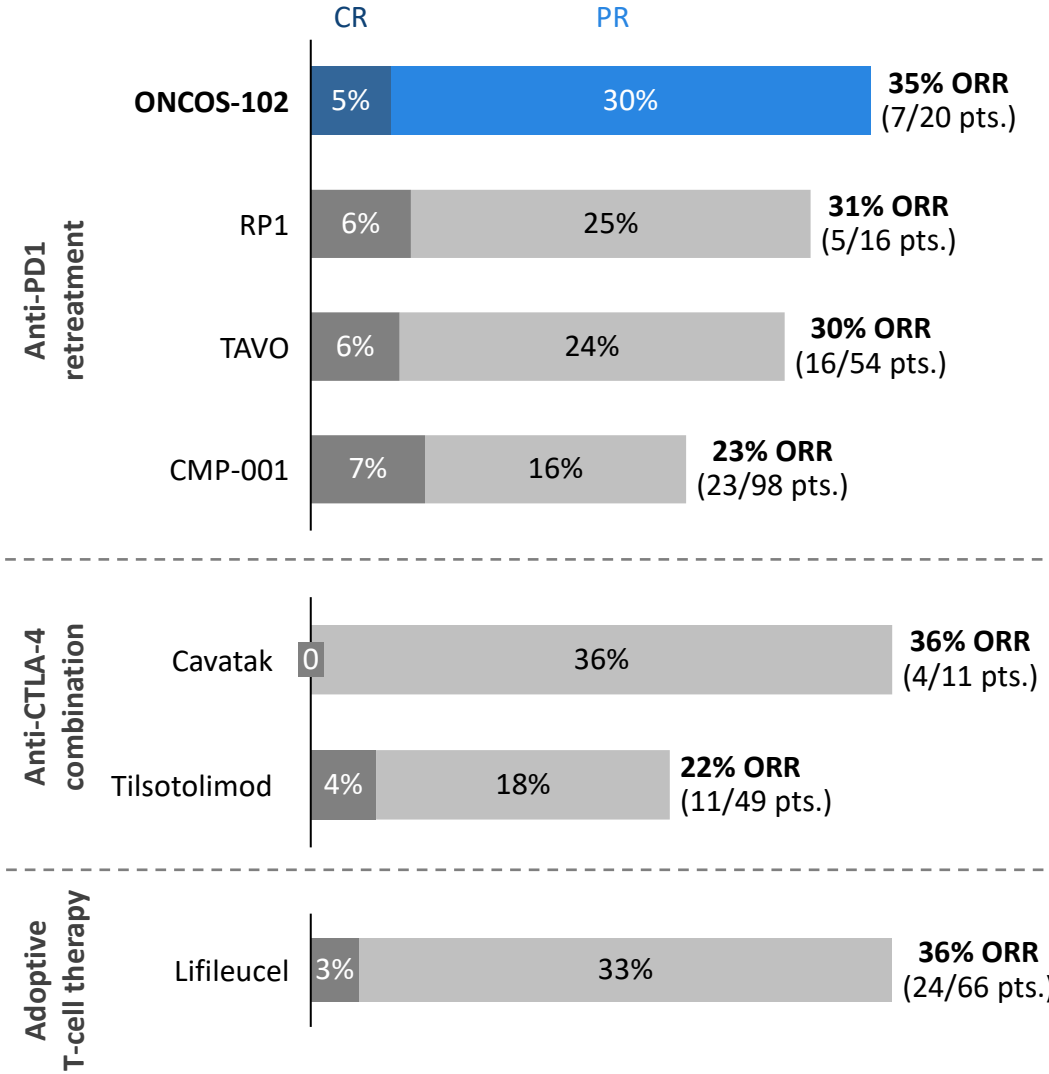


Part 2

Day 22 (n=10) & Day 64 (n=7)
Baseline (n=10)

TREM: Triggering Receptor Expressed on Myeloid cells

ONCOS-102 + Keytruda data compares well to previous reports in PD-1 refractory melanoma



Company	Comment
targovax	○ *Adenovirus expressing GM-CSF*
Replimune	○ *Herpes virus expressing GM-CSF and GALV*
oncosec IMMUNOTHERAPIES	○ *IL-12, DNA plasmid-delivered with electroporation*
CHECKMATE PHARMACEUTICALS	○ *TLR-9 agonist* ○ *Data from high-dose cohort*
	CTLA4 naïve, 10-20% ORR expected
MERCK	○ *Coxsackie virus, no transgene*
idera	○ *TLR-9 agonist*
IOVANCE BIOTHERAPEUTICS	○ *Autologous TIL therapy with IL-2* ○ *Complex and expensive manufacturing*

Targovax market analysis, January 2021.

Successful ONCOS-102 phase I trial warrants further development of PD1 combination

Safety

- ONCOS-102 is well-tolerated, with no safety concerns
- Combines well with pembrolizumab, including concomitant dosing

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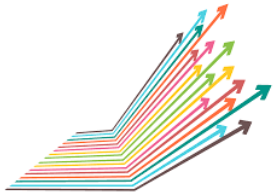
Immune activation

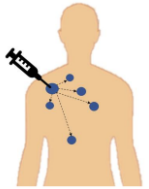


- Broad and general immune activation pattern observed in ONCOS-102 injected lesions
- Deeper biomarker and mechanistic analyses ongoing

Clinical efficacy

- Class-leading ORR of 35%
- Several responses in stage IV metastatic patients

Systemic effect



- Evidence of systemic effect in 20% of patients
- Non-injected lesion completely regressed in two patients

Melanoma: Small indication, 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 is next in melanoma? Ongoing trials and new combinations to watch

	Example compounds	Trials to watch
Novel immune checkpoint inhibitors	Anti-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, LoAd-703, ONCR-177, ONCOS-102	○ Several T-Vec trials (recently failed 1L phase III for futility) ○ Cavatak phase II 1L combination with Keytruda ○ Phase I/II - RP1 w/Opdivo, LoAd-703 w/Tecentriq
Immune stimulatory agents	TLR9, CD40, OX40, IL-2, IL-12	○ CMP-001 in PD-1 refractory, phase II combination w/Keytruda ○ Tilsotolimod in PD-1 refractory, phase III combination w/Yervoy ○ TAVO IL-12 plasmid in PD-1 refractory w/Keytruda ○ Bempegaldesleukin + nivolumab in 1L, phase III (CA045-001)
Anti-VEGFR	Lenvatinib	○ Combination with aPD1 in several melanoma patient populations ○ Phase II trial in PD-1 refractory setting
BRAFi/MEKi	Mekinist, Tafinlar	○ MEKi/BRAFi in combination with pembrolizumab in 1L BRAF V600E melanoma
TIL therapy	Lifileucel	○ TIL therapy in several melanoma patient populations ○ Pivotal phase II trial in PD-1 refractory setting

First Line Trials in Melanoma: Big Ones

Randomized, PD-1 +/- XYZ

- **LAG-3**: Nivolumab +/- Relatlimab (NCT03470922)
- **IL-2 directed**: Nivolumab +/- BEMPEG (NCT03635983)
- **VEGF**: Pembrolizumab +/- Lenvatinib (NCT03820986)

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

T-VEC: Pembrolizumab +/- T-Vec recently failed phase III for futility

First Line Trials in Melanoma: Big Ones

- **Large, randomized trials, 500-700+ patients**
- What do we need for a new standard?
  - **Overall Survival (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

Thanks!

2020 MSKCC Melanoma Disease Management Group