3

ONCOS-102 in melanoma
Dr. Alexander Shoushtari

4. ONCOS-102 in mesothelioma
5. Summary & closing

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Preliminary data from C824

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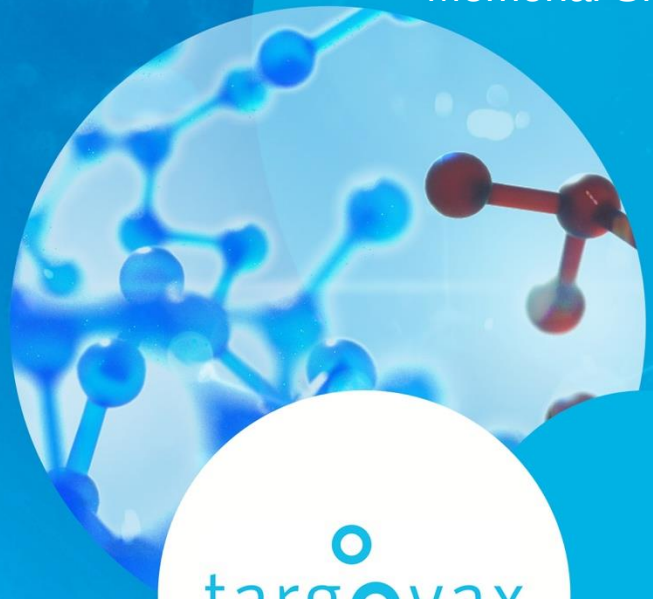
October 2018



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MELANOMA IN 2018: FRONTLINE THERAPY

PD-1 based therapy

- **2 choices**
  - Monotherapy: Pembrolizumab or Nivolumab
  - Combined Nivolumab plus Ipilimumab (CTLA-4 inhibitor)
- **45 - 60% objective response rate**
- **Responses last 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 monotherapy versus combined therapy**
  - Monotherapy: 1 in 4 require steroids
  - Combined Nivo + Ipi: 3 in 4 require steroids

MELANOMA IN 2018: FRONTLINE THERAPY

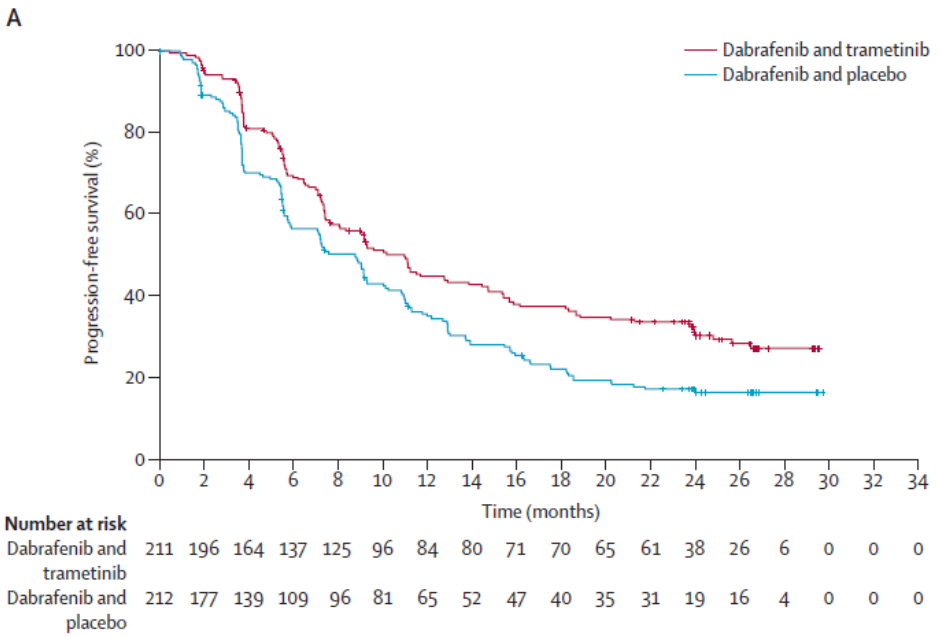
BRAF-MEK Inhibition

- **Only available for 40-50% with BRAF V600 mutant melanoma**
- **60-70% objective response rate**
- **Responses last average of 12-15 months**
- **Adverse events (AEs) not directly related to immune system**
  - Diarrhea
  - Liver inflammation
  - Rash
  - Fevers, chills
  - Muscle/joint aches
- **If BRAF-MEK stopped, adverse events stop**

MELANOMA IN 2018: NEEDS

Resistance to Standard Therapies

- **BRAF-MEK therapy:** majority of initial responders will progress (secondary resistance)



Long et al, Lancet 2015

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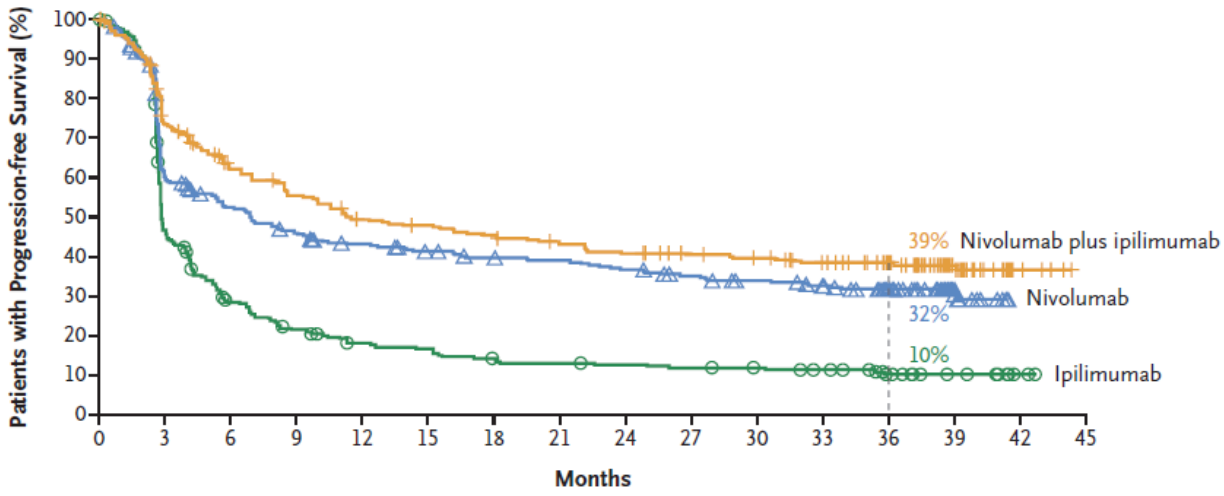
MELANOMA IN 2018: NEEDS

Resistance to Standard Therapies

- **BRAF-MEK therapy:** majority of initial responders will progress (secondary resistance)

- **PD-1 based therapy:**
  - 30-40% will have primary resistance
  - 25-35% will have secondary resistance



MELANOMA IN 2018: NEEDS

Resistance to Standard Therapies

- **BRAF-MEK therapy:** majority of initi
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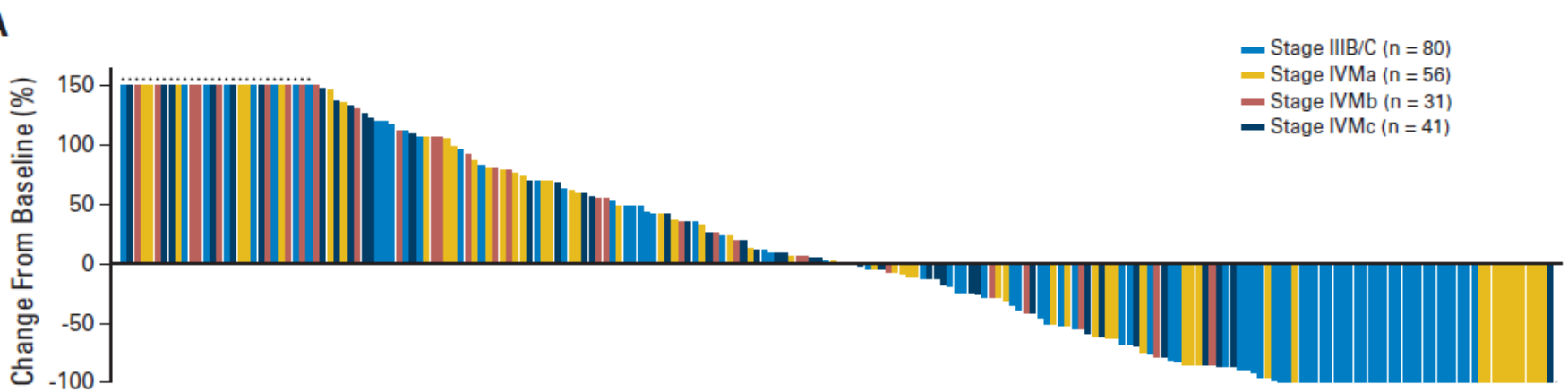

- PD
  -
  - resistance

- **Talimogene Laherparepvec**
  - 40% primary resistance in injected lesions
  - 85% resistant in distant lesions
  - Takes 10 injections on average to respond as monotherapy

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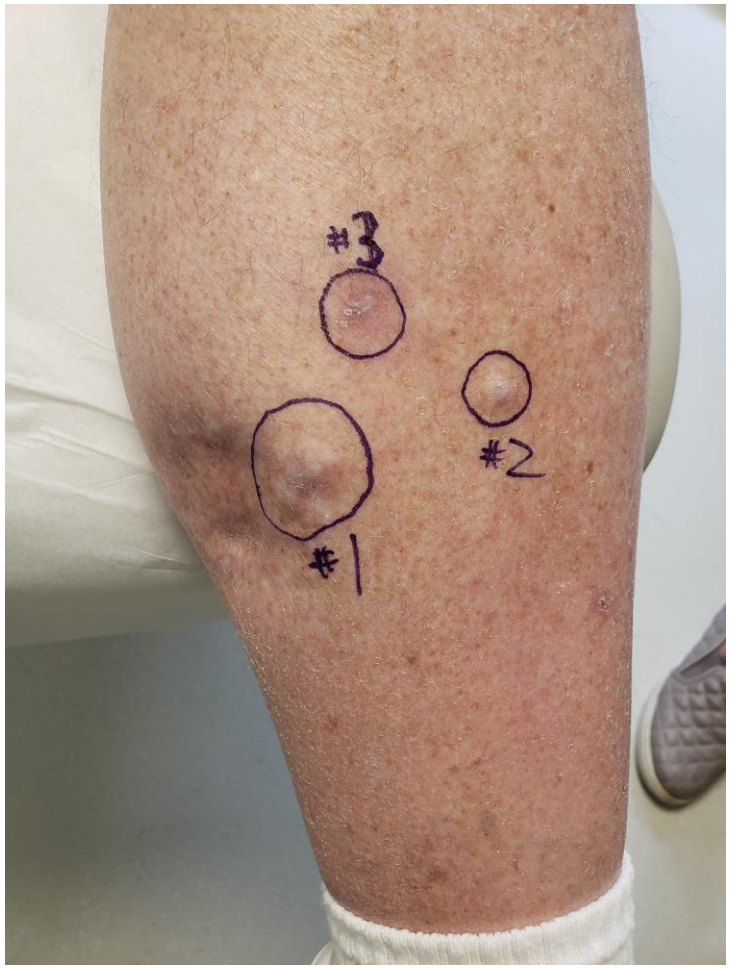
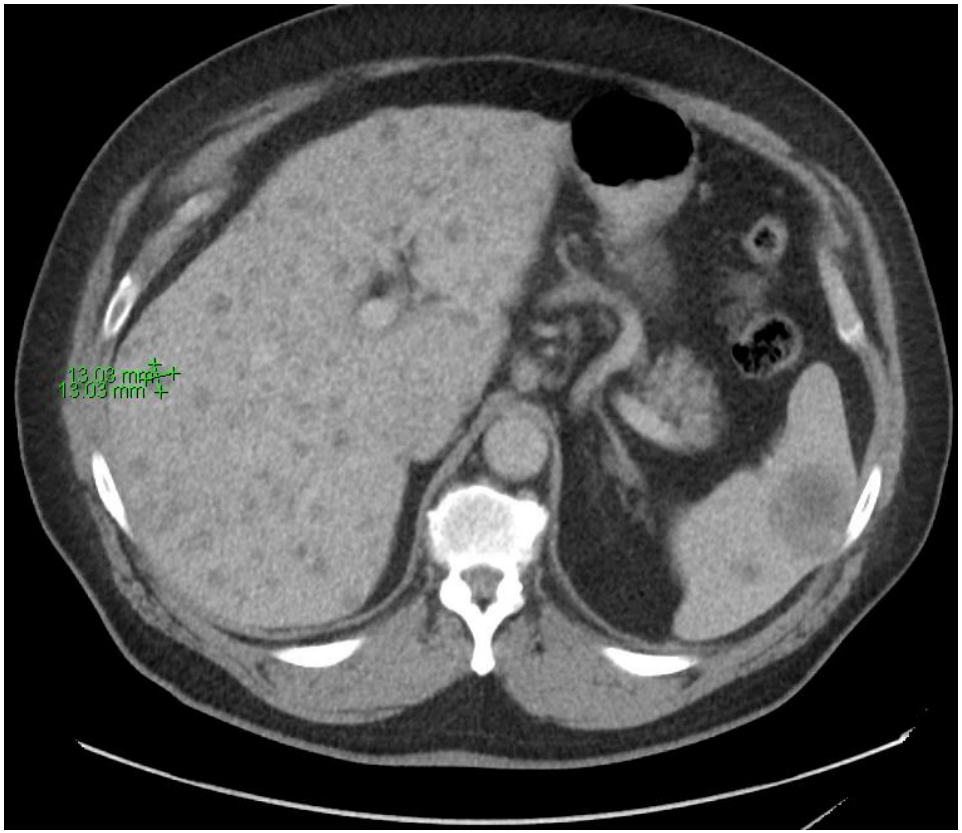
MELANOMA IN 2018: NEEDS

Not all resistance is treated alike!





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MELANOMA IN 2018: OPTIONS POST-PD-1

Standard Options

- **After PD-1 monotherapy**
  - BRAF-MEK, if V600 mutant
  - Nivolumab plus ipilimumab
  - Ipilimumab alone
  - Cytotoxic chemotherapy
  - T-VEC if injectable
- **After Nivolumab plus Ipilimumab**
  - BRAF-MEK, if V600 mutant
  - Cytotoxic chemotherapy
  - T-VEC if injectable
- **If local progression only**
  - Surgery
  - Radiation therapy

Non-standard options

- **Clinical Trials (selected)**
  - PD-1 plus
    - LAG-3 inhibitor
    - OX40 agonist
    - GITR agonist
  - Tumor Infiltrating Lymphocyte trials
  - Injectable trials
    - ONCOS-102 + pembro
    - TVEC + pembro
    - Coxsackievirus + pembro
    - TLR9 agonist (tilsotolimod) + ipilimumab
- **Off-label uses**
  - BRAF + MEK + PD-1
  - T-VEC + PD-1 inhibitor
  - Radiation + PD-1 +/- Ipilimumab

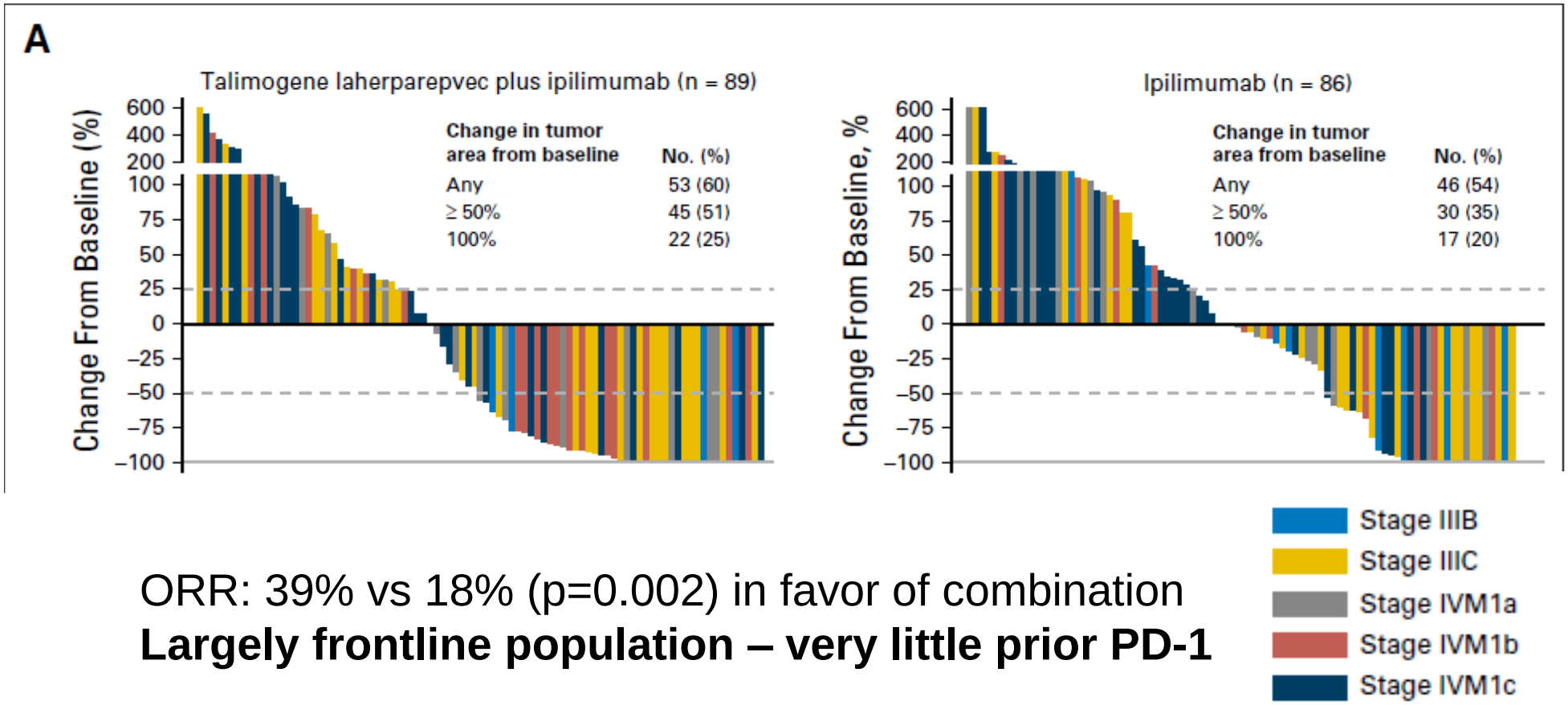
MELANOMA IN 2018: CHALLENGES

- **After PD-1 progression, no "one size fits all" approach**
  - Nivolumab plus LAG-3 – 10-15% response rate
  - IDO inhibitors had a negative frontline trial
- **Rightly or wrongly, many physicians want an excuse to avoid ipilimumab**
  - 20-30% response rate, can be durable
  - Significant toxicity
- **Injectable combinations may represent a happy medium**
  - Overcome lack of recognition by direct injection of agent into tumor
  - Activate innate and adaptive immune system → "domino effect"
  - ?Fewer off-target effects to reduce systemic toxicity

MELANOMA: INJECTABLE COMBINATIONS TO DATE

T-VEC +/- Ipilimumab (Chesney et al, J Clin Oncol 2017)

TVEC: day 1, 22, then every 2 weeks



ORR: 39% vs 18% (p=0.002) in favor of combination

Largely frontline population – very little prior PD-1

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MELANOMA: INJECTABLE COMBINATIONS TO DATE

Cocksackie virus CVA21 + pembro (CAPRA, Silk et al, AACR 2017)

- **Largely PD-1 naïve**
- Injections: D1, 3, 5, 8, every 3 weeks for up to 19 total
- 8 of first 11 evaluable patients with objective responses

Toll-Like Receptor 8/9 Agonist + Ipilimumab (Diab et al, ASCO 2018)

- **Already received PD-1 blockade** – only study to date
- Only 3 of 26 were stage 3; 11 (42%) M1c
- 8 of 21 patients responded (38%)
  - 2 CR
  - 6 PR
  - 8 SD
  - 5 PD

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ONGOING TARGOVAX STUDY at MSKCC

A Pilot Study of Sequential ONCOS-102 and Pembrolizumab in Patients with Advanced or Unresectable Melanoma Progressing after PD1 Blockade

Deliveries:
- ORR data on 6 patients
- 4/4 patients biopsy data: TILs (CD3+, CD4+ and CD8+ T cells) – Day 1, 22 and 64
- 4/4 patients cytokines: IFNgamma, TNFa, IL6 - Day 1, 4, 8/W3/W9/W18
- 4/4 patients PBMC: T cell activation/exhaustion - Day 1, W 3, 8/9
- 1st safety review of 4 pats – there were no issues

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STUDY OBJECTIVES

Primary Endpoint

- Safety of sequential administration of 3 doses of ONCOS-102 followed by 8 doses of pembrolizumab

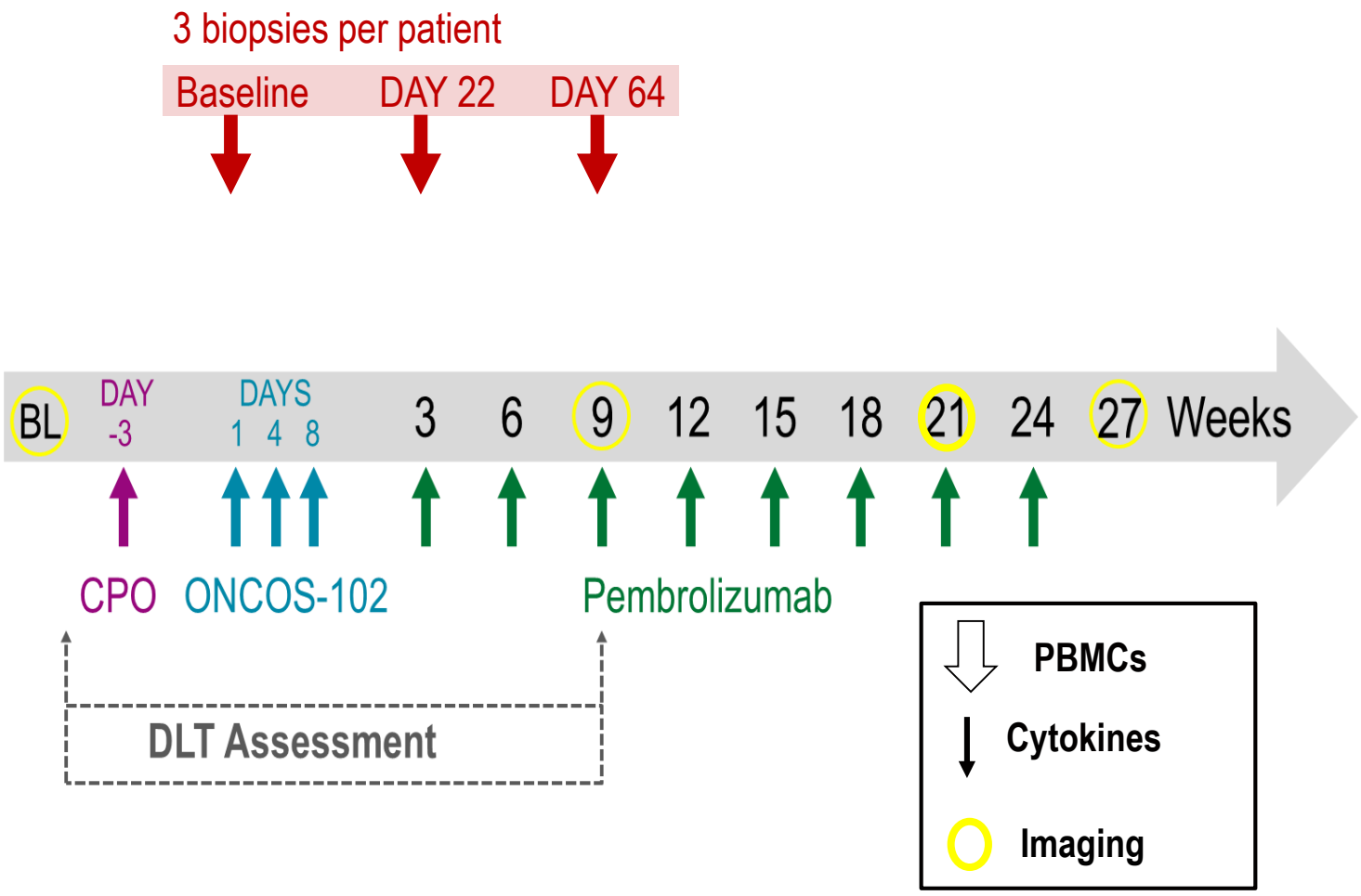
Exploratory Endpoints

- Analysis of mutation rate in relation to response
- Changes in T cell receptor clonality
- Gene expression analysis in biopsied tissue

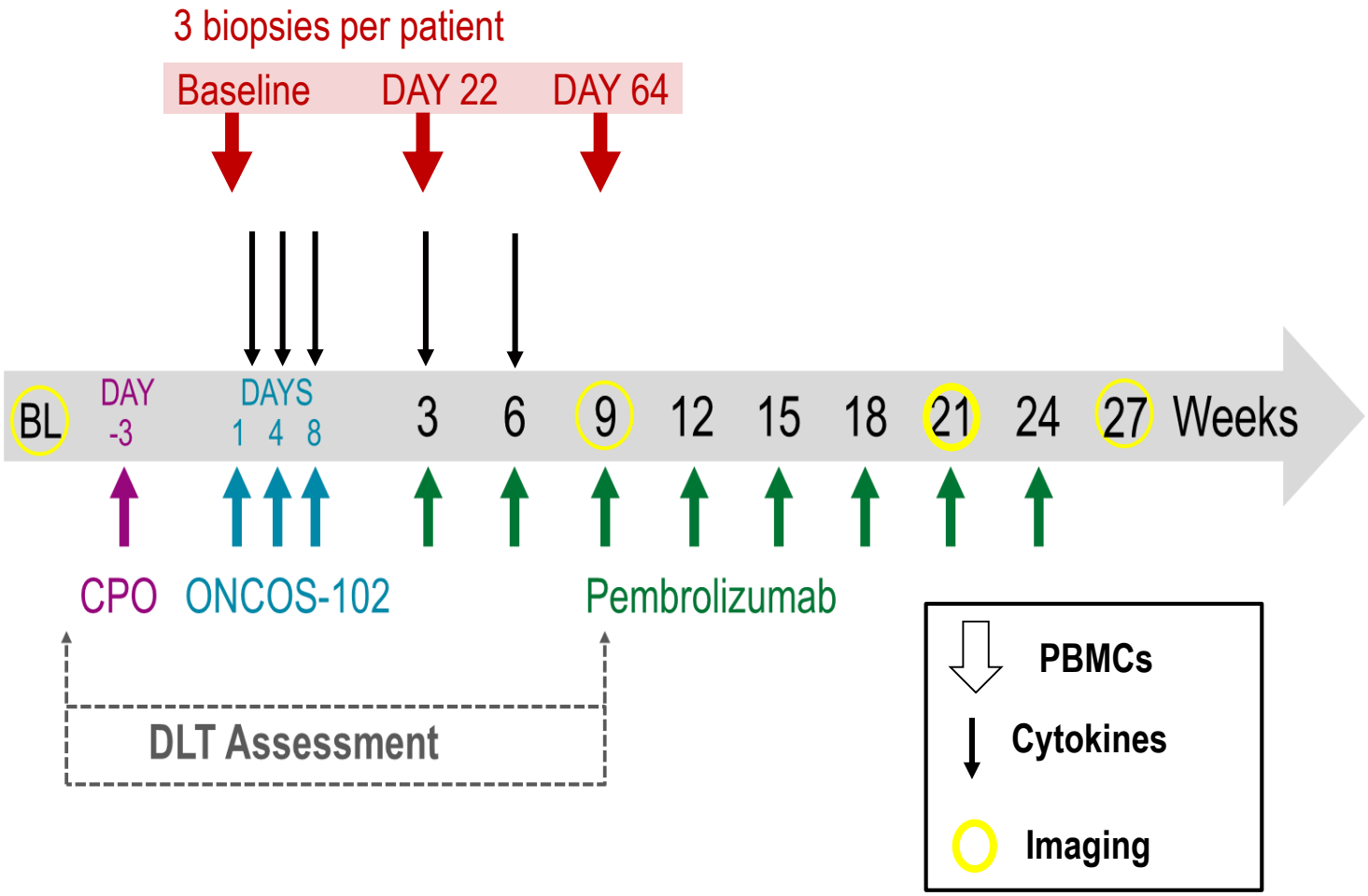
Secondary Objectives

- Objective responses by RECIST 1.1 and irRECIST
- Progression-free survival
- Change in size of individual lesions
- Immune subsets in tumor and plasma, changes over time

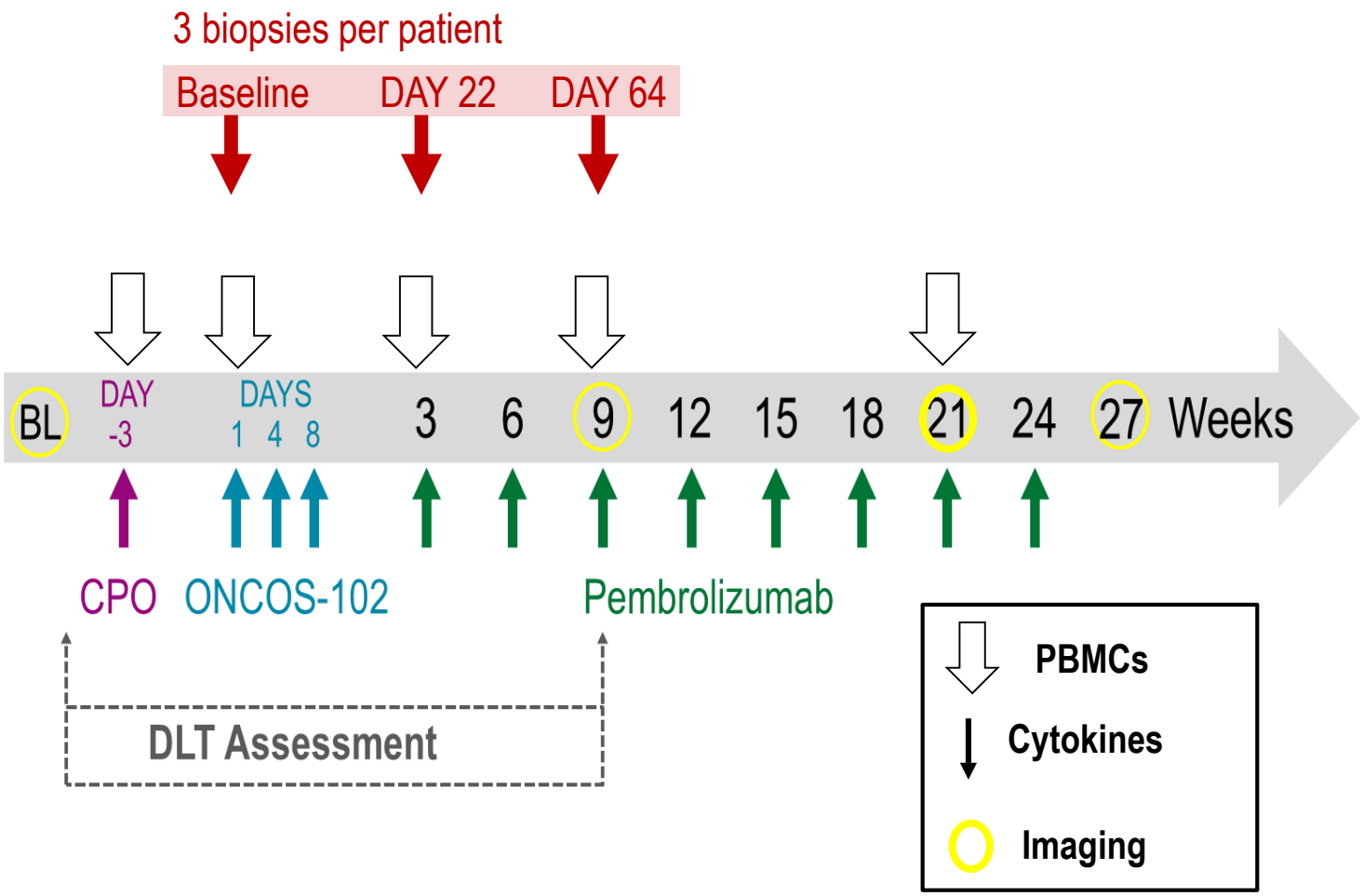
STUDY SCHEMA



STUDY SCHEMA



STUDY SCHEMA



WHAT REPRESENTS SUCCESS (TO A MELANOMA ONCOLOGIST)?

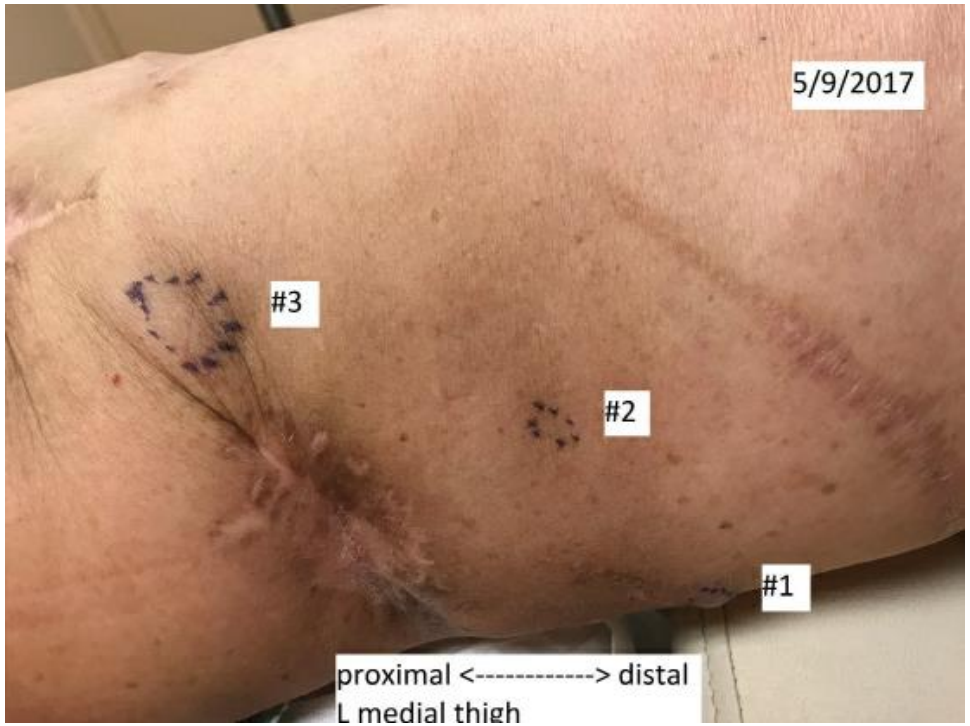
- Ability to administer the drug safely
- Evidence of preliminary efficacy
- Access to tissue and biomarker data to refine your therapeutic strategy moving forward

87 year old female

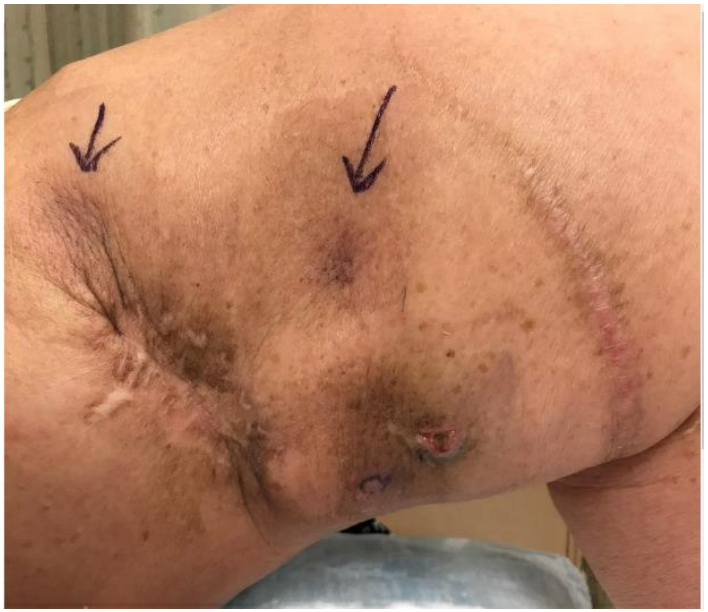
Surgery, Keytruda, T-VEC, Radiotherapy prior study

ORR: PD (not received full dose of ONCOS-102)

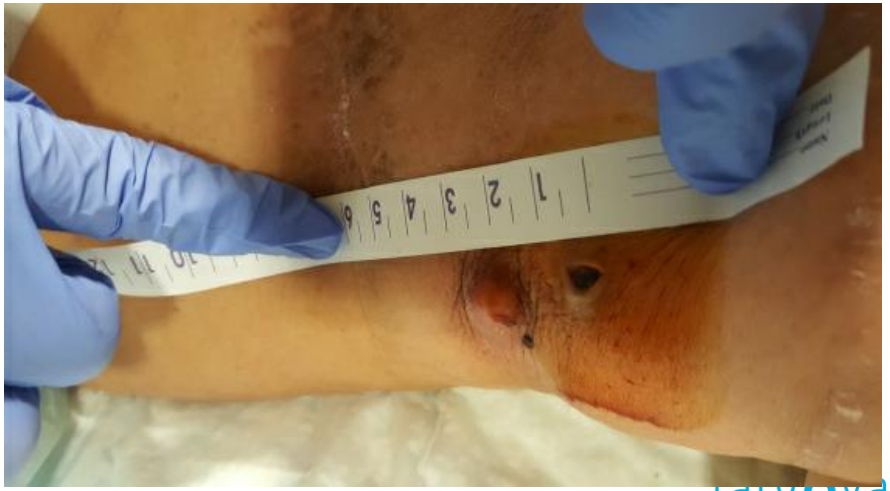
Baseline



Day 10



Day 22

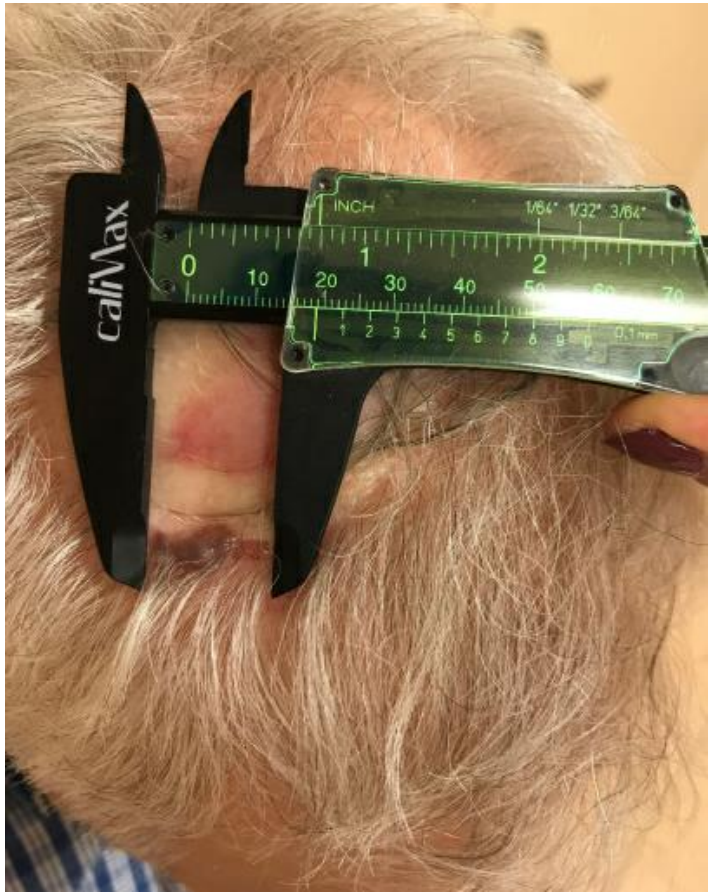


73 year old male

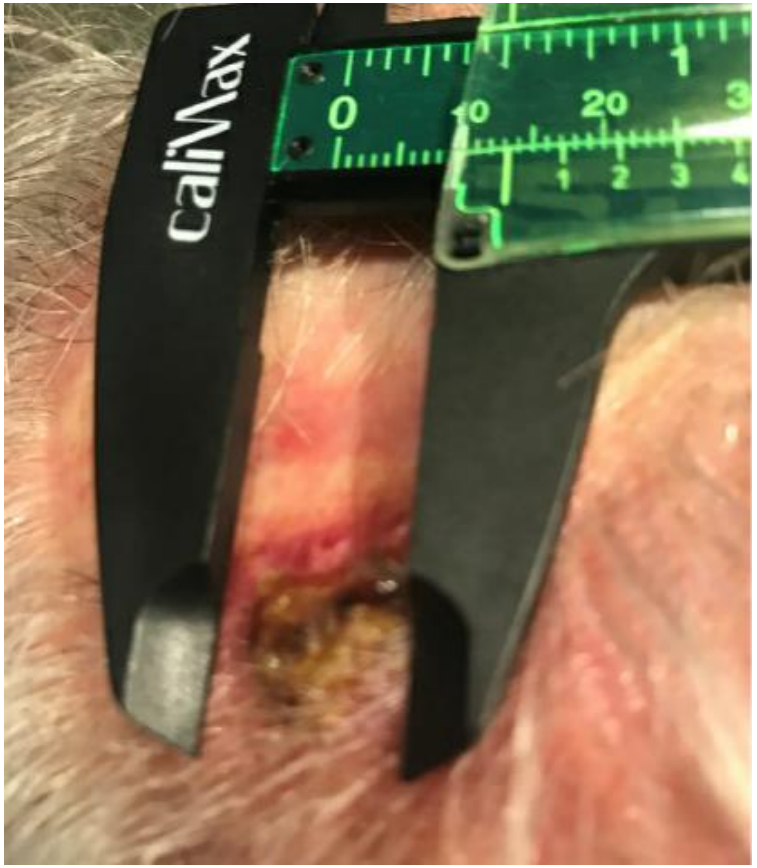
Surgery, Keytruda prior study

ORR: PD (not received full dose of ONCOS-102)

Baseline



Day 22



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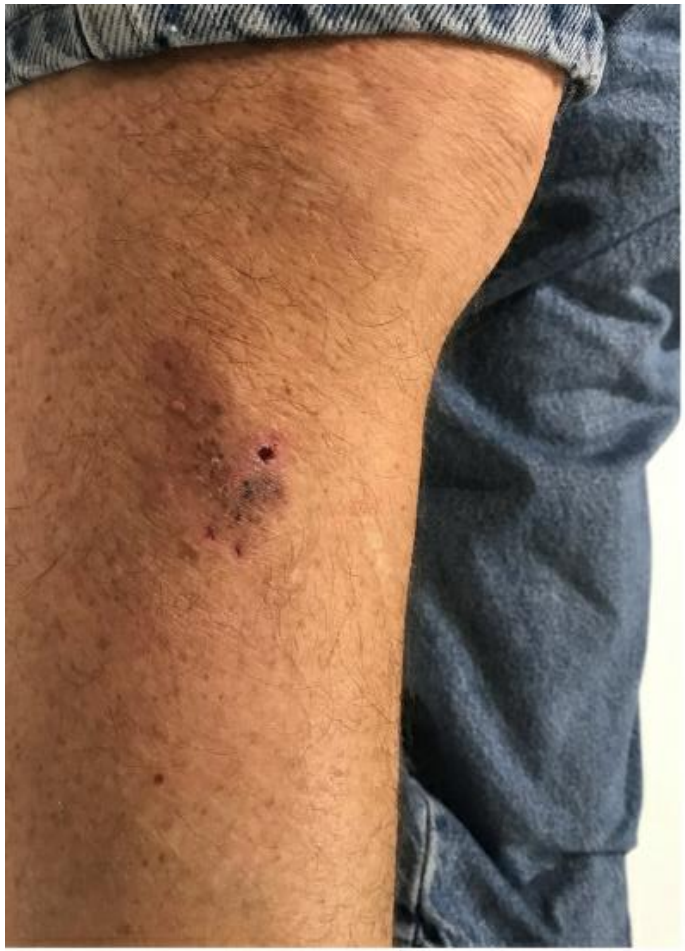
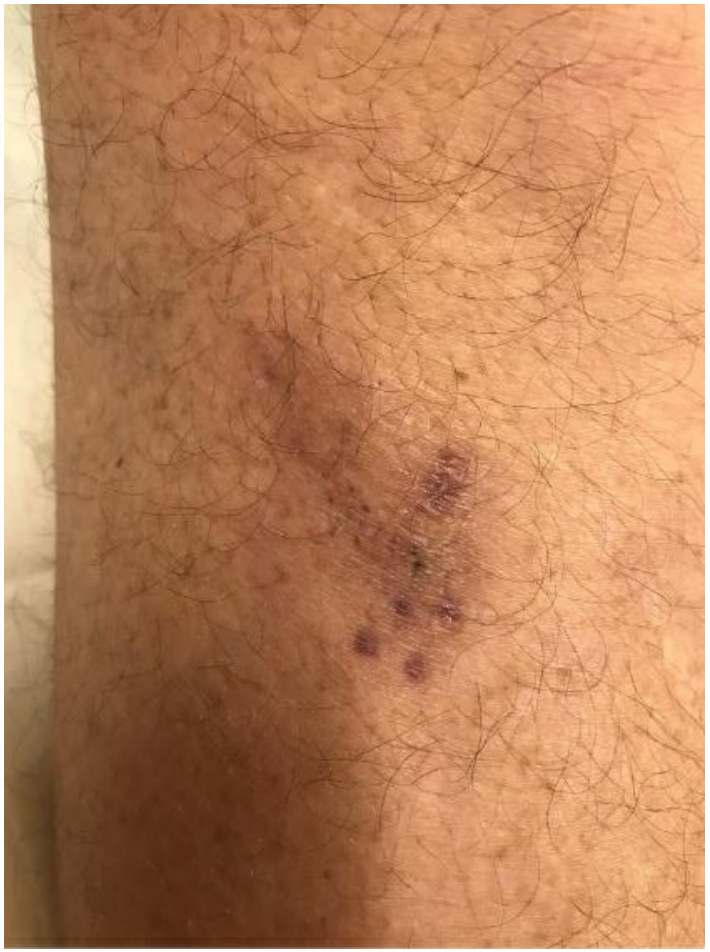
60 year old male

Surgery, Yervoy, Keytruda prior study

ORR: CR (after only 2 Keytruda infusions)

Baseline **Day 22** **Day 63**





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3 MORE PATIENTS

79 year old male; had Yervoy, Keytruda, T-VEC prior study

- Shrinkage in injected lesion but new distant lesion
- ORR: PD

74 year old female; had surgery and Opdivo prior study

- ORR: PD

78 year old female; had Yervoy, Opdivo, Keytruda prior study

- ORR: PD

EFFICACY, N=6

Demographics

- **Age:** 60 – 87 (median 76)
- **Stage**
  - IIIB/C: 5 of 6
  - IV: M1C, 1 of 6
- **Prior PD-1 blockade:** 100%
- **Prior Ipilimumab:** 50%
- **Prior Injectable:** 50%
- **Prior BRAF:** 50% (2 of 3 intolerant)
- **Median prior lines**: 2.5 (range: 1-4)

Efficacy

- **Complete Response: 1/6, 12+ mo**
- **Partial Response: 0/6**
- **SD: 0/6**
- **PD: 5/6**

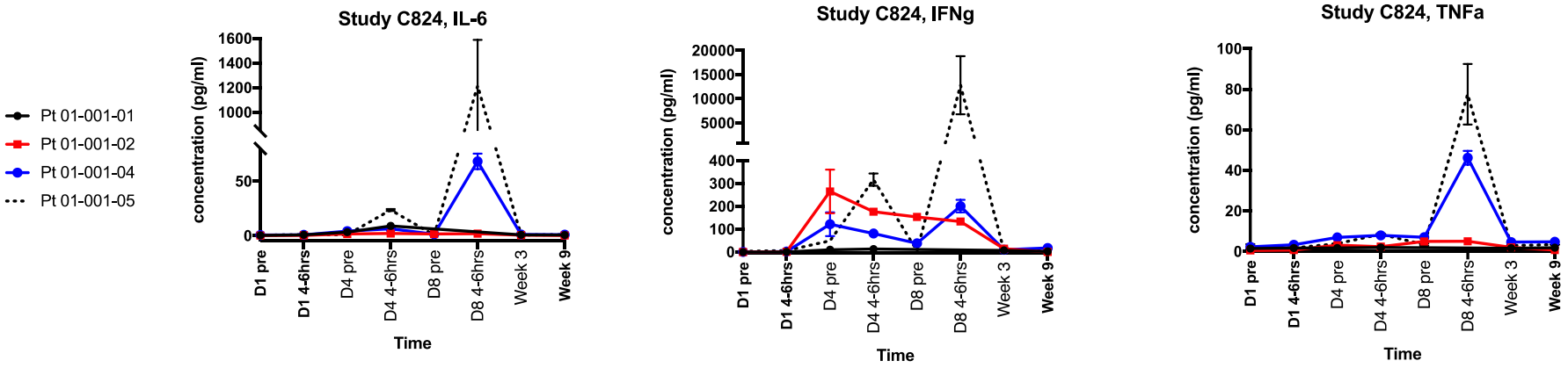
- **Anecdotally:** At least 3 patients with “PD” had transient shrinkage in the injected tumor

ONCOS-102 INDUCED INCREASE OF CYTOKINES IN ALL PATIENTS (tested to date n=4)

Summary on cytokines analyses (D 1, 4, 8, W3, 9/18):

- Increase of pro-inflammatory cytokines (IFN-y, TNF-a, IL-12p40, GM-CSF) after ONCOS-102 administration (4 out of 4)
- Increase of pro-inflammatory cytokines (IL-6 and IL-8) after ONCOS-102 administration (3 out of 4)
- Temporarily elevation level of IL-10 after second ONCOS-102 administration (3 out of 4 patients)
- Profound increase of IL-6, TNFa and IFNg (001-01-005)

The treatment with ONCOS-102 induces innate immune responses



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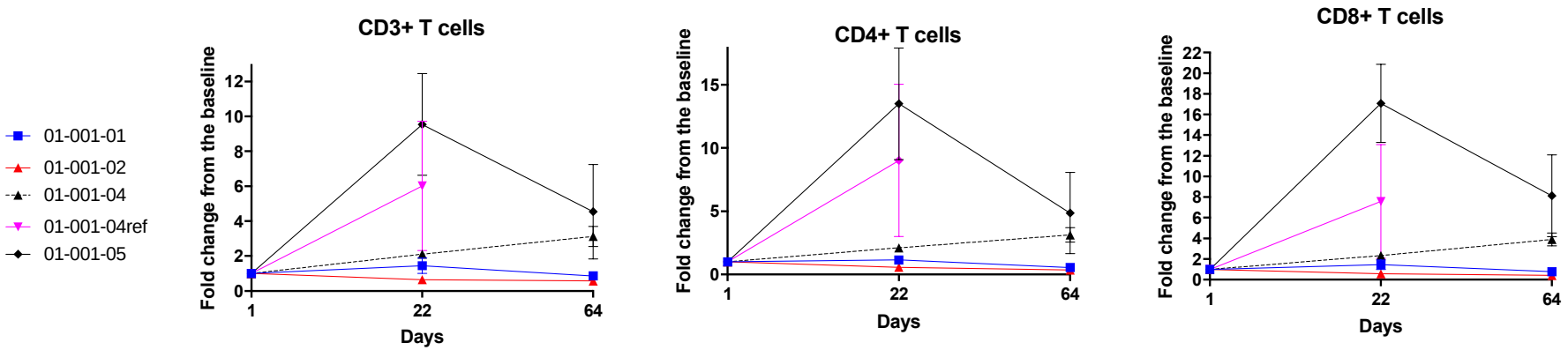
T CELL INFILTRATES ON MULTIPLEX IHC INCREASE WITH ONCOS-102



Patient with CR had highest relative increase of CD3+, CD4+, CD8+ cells

2 patients with reduced dose of ONCOS-102 had lower relative increases

Non-injected lesion seen with increase of CD3+, CD4+ and CD8+ T cells

PINK: un-injected lesion

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ONCOS-102 INDUCED CANCER ANTIGEN SPECIFIC T-CELLS

Measured by IFN gamma ELISPOT in PBMCs (baseline vs. post-treatment samples)

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LESSONS LEARNT AND NEXT STEPS

- We can inject ONCOS-102 safely and follow with pembrolizumab in patients with melanoma that has recurred despite prior PD-1 blockade
- There is preliminary efficacy in a patient with PD-1 refractory in-transit disease – associated with the most profound activation of both innate and adaptive immune cells
- Correlative analyses in the first 4 patients provide evidence supporting the proposed mechanism of action
- For larger baseline lesions, transient shrinkage is seen when injected with 3 doses of ONCOS-102, but it does not appear to persist
- If we could inject more doses of ONCOS-102, more lesions are likely to respond

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NEW SCHEMA: 12 ADDITIONAL PATIENTS

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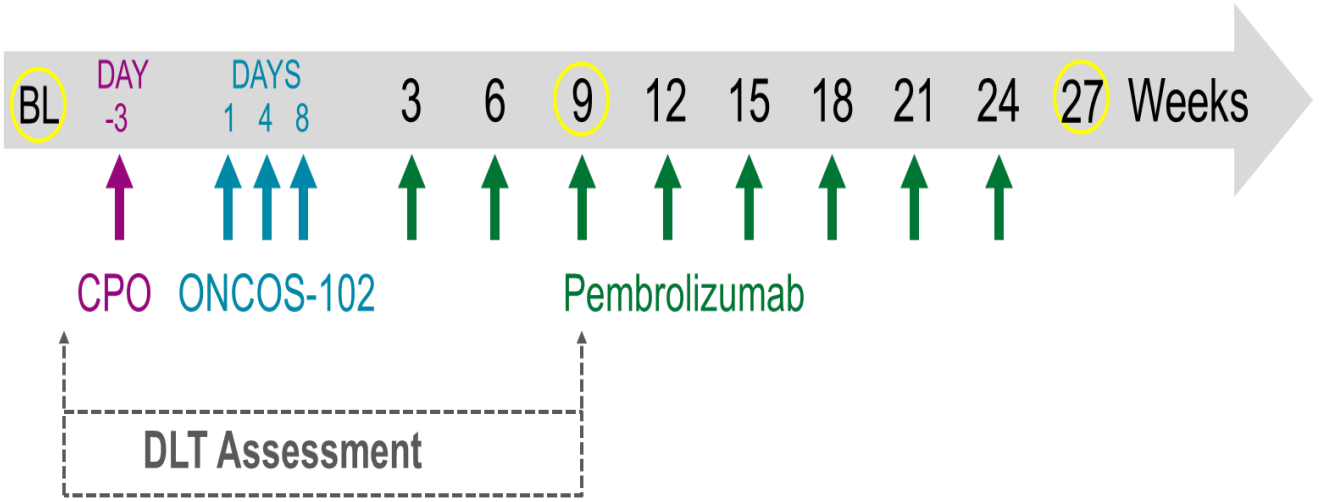

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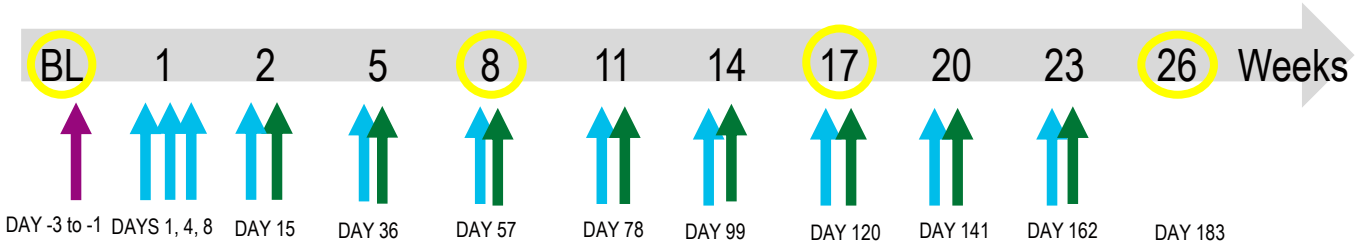

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SUMMARY

- ONCOS-102 safe and well tolerated
- ORR in 1/6 patients in pre-treated population
  - Patients were not ”cherry-picked” and likely to represent true population
  - The only variable that we changed is 3 doses of ONCOS-102
- Mechanism of action is supported by preliminary correlative data
  - Increase in pro-inflammatory cytokines associated with improved outcomes to PD-1
  - Increase in tumor-infiltrating CD4+/8+ T cells
- Solid rationale for increasing the number of ONCOS-102 injections
  - Increase ability to shrink injected tumor
  - Mirror other trials (e.g. TVEC, TLR9) that have shown some visceral efficacy
  - now being approved at 2 additional US sites

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