Combination Immunotherapies: Melanoma

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Objectives

- Understand how combination immunotherapies are currently being used to treat patients with metastatic Melanoma
- Understand the clinical evidence supporting the use of combination immunotherapies to treat patients with metastatic Melanoma
- Be informed and updated on combination immunotherapies in development focusing on metastatic Melanoma

Immunotherapies are being used today to treat a number of different tumor types

Prostate Cancer

- e.g. Sipuleucel-T

Melanoma

- e.g. Ipilimumab, pembrolizumab, nivolumab, T-Vec

Non-Small Cell Lung Cancer

- e.g. Nivolumab, pembrolizumab

Renal Cell Carcinoma

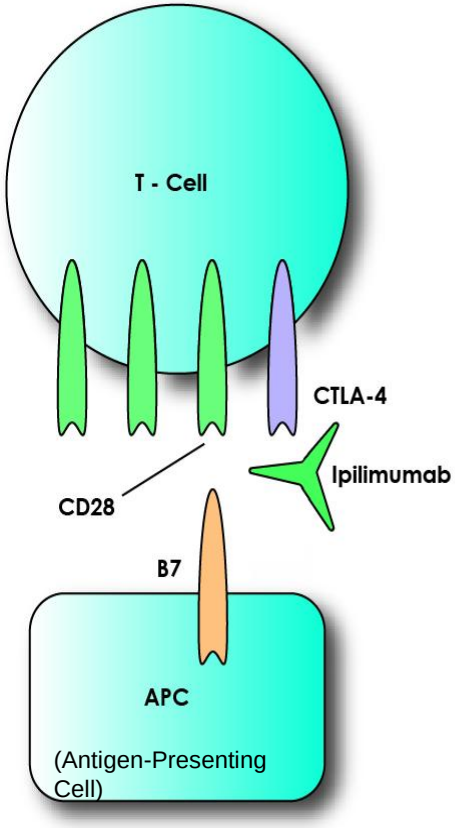
- Nivolumab

Immunotherapy – Checkpoint Inhibitors

Tumors escape detection from the immune system by expressing "checkpoint" proteins on their cell surface; targeting and inhibiting these cell surface proteins enhances the immune response to the tumor

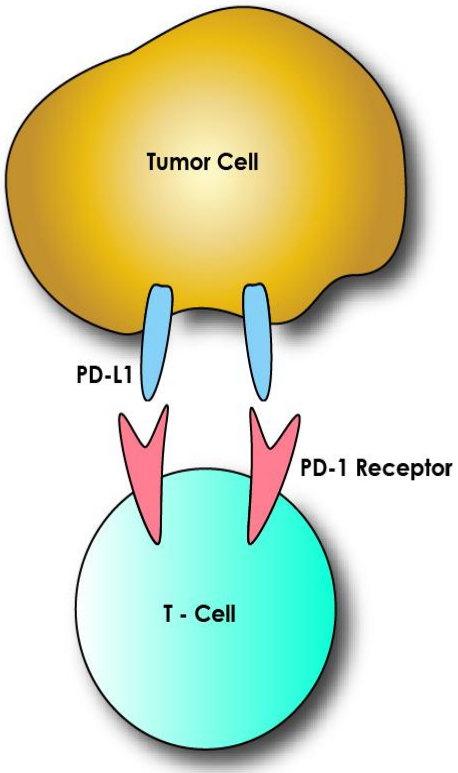
CTLA-4 Inhibition

ACTIVATION



PD-1/PD-L1 Inhibition

INHIBITION



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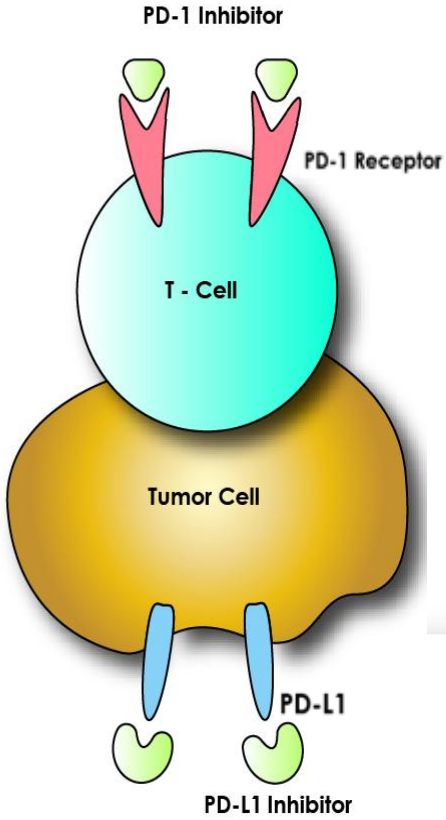


Checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab are FDA approved to treat patients with metastatic melanoma

Yervoy (ipilimumab)

Mechanism of Action: human, monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) on T cells

Melanoma Indication: the treatment of unresectable or metastatic melanoma

Opdivo (nivolumab)

Mechanism of Action: human, monoclonal antibody directed against the programmed death-1 (PD-1) receptor of the T Cell

Melanoma Indication:

- Monotherapy: the treatment of patients with BRAF V600 wild-type or BRAF V600 mutation positive unresectable or metastatic melanoma
- Combination: in combination with ipilimumab for unresectable or metastatic melanoma

Keytruda (pembrolizumab)

Mechanism of Action: human, monoclonal antibody directed against the programmed death-1 (PD-1) receptor of the T Cell

Melanoma Indication: the treatment of patients with unresectable or metastatic melanoma

Combination immunotherapy is recommended for both 1st line and 2nd line/subsequent metastatic or unresectable melanoma

Metastatic or Unresectable Melanoma δ

1st Line	• *Immunotherapy* ➢ *Anti PD-1 monotherapy* ○ *Nivolumab* ○ *Pembrolizumab* ➢ *Combination immunotherapy* ○ *Nivolumab/ipilimumab*	• *Combination therapy** ➢ *Dabrafenib/trametinib* ➢ *Vemurafenib/cobimetinib* • *Single agent therapy** ➢ *Vemurafenib* ➢ *Dabrafenib*
2nd Line or subsequent	• *Immunotherapy* ➢ *Monotherapy* ○ *Nivolumab* ○ *Pembrolizumab* ○ *Ipilimumab* ➢ *Combination immunotherapy* ○ *Nivolumab/ipilimumab*	• *Combination therapy** ➢ *Dabrafenib/trametinib* ➢ *Vemurafenib/cobimetinib* • *Single agent therapy** ➢ *Vemurafenib* ➢ *Dabrafenib* • *High-dose IL-2 or Biochemotherapy or cytotoxic agents or imatinib (patients with C-KIT mutations)*

(source: NCCN Clinical Practice Guidelines in Oncology, Melanoma, Version 2.2016)

** Targeted therapy if BRAF mutated*

δ Additional systemic therapies not represented include the following cytotoxic regiments: dacarbazine, temozolomide, paclitaxel, albumin-bound paclitaxel, carboplatin/paclitaxel; Biochemotherapy: dacarbazine or temozolomide, and cisplatin or carboplatin with or without vinblastine or nitrosourea, and IL-2 and interferon alfa-2b; Biochemotherapy for adjuvant treatment of high risk disease: Dacarbazine, cisplatin, vinblastine, IL-2, and interferon alfa-2b; NCCN also recommends clinical trials for 1st or 2nd line/subsequent therapy

Melanoma - Nivolumab in combination with ipilimumab

Use of nivolumab in combination with ipilimumab is supported by clinical evidence from Phase II and Phase III, double-blind, randomized trials in patients with previously untreated, unresectable or metastatic melanoma

Phase II, Multicenter, double-blind, randomized trial, nivolumab in combination with ipilimumab vs. ipilimumab:

Patients previously untreated, unresectable, or metastatic melanoma, wild type BRAF V600	**Nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) every 3 weeks for 4 doses followed by single agent nivolumab (3 mg/kg) every 2 weeks (n=72)**	**Ipilimumab (3 mg/kg) every 3 weeks for 4 doses followed by placebo every 2 weeks (n=37)**
Objective Response Rate	CR=17%; PR=43%	CR=0%; PR=11%
Median Progression-free Survival	8.9 months	4.7 months

Similar results were observed in patients with the BRAF mutation

(source: Hodi et al., 2015)

Melanoma - Nivolumab in combination with ipilimumab

Use of nivolumab in combination with ipilimumab is supported by clinical evidence from Phase II and Phase III, double-blind, randomized trials in patients with previously untreated, unresectable or metastatic melanoma

Phase III: Nivolumab in combination with ipilimumab vs. single agent nivolumab vs. ipilimumab in combination with placebo:

Patients previously untreated, unresectable, or metastatic melanoma	Nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) every 3 weeks for 4 doses followed by single agent nivolumab (3 mg/kg) every 2 weeks (n=314)	Nivolumab (3 mg/kg every 2 weeks (n=316)	Ipilimumab (3 mg/kg) every 3 weeks for 4 doses followed by placebo every 2 weeks (n=315)
Median Progression-free Survival (PFS)	11.5 months	6.9 months	2.9 months
Objective Response Rate (ORR)	CR = 8.9%; PR = 41%	CR = 8.5%; PR = 31%	CR = 1.9%; PR = 12%
Duration of Reponse: proportion ≥ months in duration	76%	74%	63%

(source: Opdivo (nivolumab) FDA approved label, Bristol-Myers Squibb; Larkin et al., 2015)

Adverse events – nivolumab in combination with ipilimumab

Phase III: Nivolumab in combination with ipilimumab vs. single agent nivolumab vs. ipilimumab in combination with placebo; previously untreated, unresectable or metastatic melanoma

Treatment-related adverse events	Nivolumab + Ipilimumab (n=313)	Nivolumab (n=313)	Ipilimumab (n=311)
Grade 3 or 4	55.0%	16.3%	27.3%

Most Common Grade 3 or 4 treatment-related adverse events (>5% Nivolumab + Ipilimumab arm)	Nivolumab + Ipilimumab (n=313)	Nivolumab (n=313)	Ipilimumab (n=311)
Diarrhea	9.3%	2.2%	6.1%
Increase in alanine amino-transferase level	8.3%	1.3%	1.6%
Increase in aspartate amino-trasferase level	6.1%	1.0%	0.6%
Colitis	7.7%	0.6%	8.7%

- Treatment-related adverse events of any grade that led to discontinuation of therapy was 36.4% in the nivolumab + ipilimumab group, 7.7% in the nivolumab group, and 14.8% in the ipilimumab group
- One death was reported in the nivolumab group (neutropenia) and the ipilimumab group (cardiac arrest), but none in the nivolumab + ipilimumab group

According to investigators, "Adverse events were manageable with established treatment guidelines, and most select adverse events resolved with the use of immune-modulatory agents."

(source: Larkin et al., 2015)

In addition to melanoma, nivolumab in combination with ipilimumab is being studied in a number of tumor types

- Melanoma
- Lung Cancer
- Myelodysplastic Syndromes
- Lymphoma
- Multiple Myeloma
- Sarcomas
- Renal Cell Carcinoma
- Pancreatic Cancer
- Gastric Cancer
- Bladder Cancer
- Ovarian Cancer
- Glioblastoma
- Colorectal Cancer
- Liver Cancer
- Breast Cancer

Case Report 1:
Metastatic Mucosal Melanoma

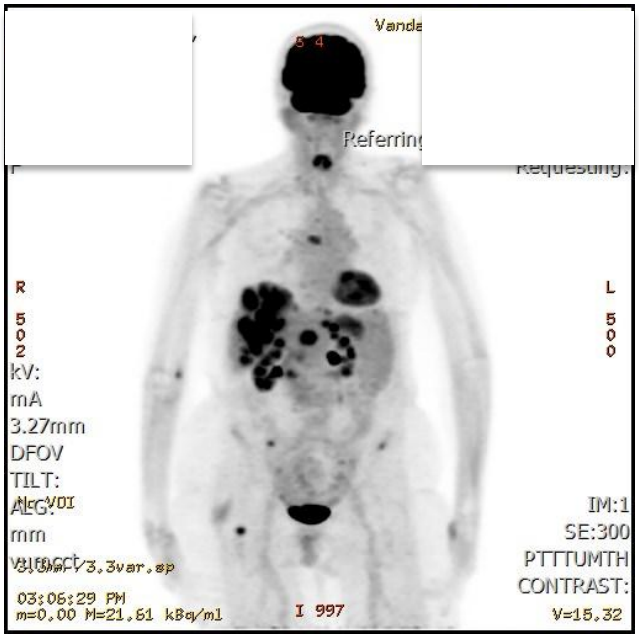
- 88-year-old white female
- Left-nasal bloody discharge and pain in March 2014
- Left ethmoid mass resection 3/23/14-musosal melanoma pT3N0M0, 13 mitoses/mm2
- Adjuvant XRT for close margins
- Re-resection 10/23/13 for in situ residual melanoma-followed by radiographic surveillance

Case Report 1:

Metastatic Mucosal Melanoma

- Developed new pain in RUQ, April 2015
- Required 120 mg of long-acting morphine 3X daily
- ECOG performance status=2
- PET/CT scan 05/08/2015

LDH = 499 (normal <225)
WBC = 13.6, ANC=11.9,
HCT = 40, Plt = 554
Alk Phos = 225 (<110),
AST = 36, ALT = 19
PET/CT: bones, liver, lung, soft tissue, nasal cavity



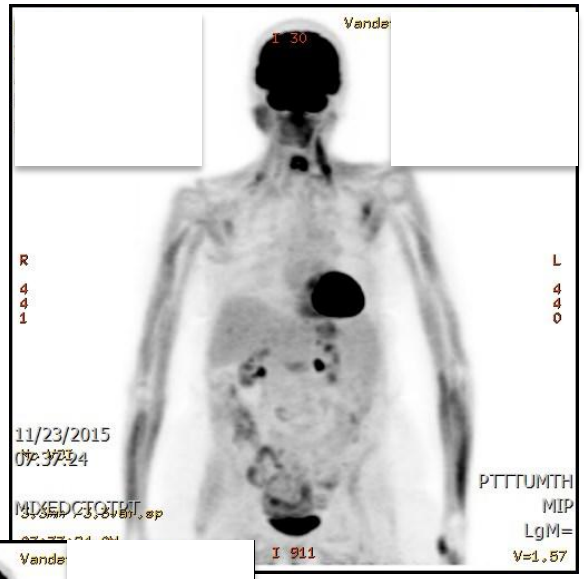
Case Report 1:
Metastatic Mucosal Melanoma

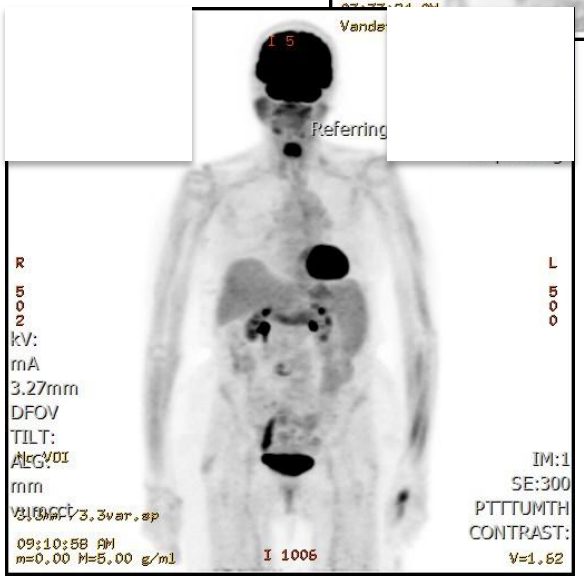
- BRAF, c-kit, NRAS wt
- Ipilimumab 3 mg/kg+
  Nivolumab 1mg/kg (05/21/15)
- C2D1 06/15/15
- C3D1 held for grade 2
  mucositis, arthralgias,
  AST 160 (grade 2), ALT 90
- Steroid taper 4 weeks, starting 1 mg/kg daily po, PPI bid, Bactrim DS TIW x 2 weeks

Case Report 1:

Metastatic Mucosal Melanoma

- Toxicity resolved in 2 weeks on steroids, finished taper
- PET/CT 08/19/2015-CR
- Started nivolumab 3 mg/kg (09/30/15)-now 11 more doses
- Continues with grade 1 mucositis, arthralgias, LFTs nl.
- PET/CT 11/23/15-CR





Conclusions:

Rapidly Progressing Metastatic Melanoma including Mucosal Melanoma

- Ipilimumab/Nivolumab combination may be as fast acting as targeted BRAF or c-kit targeted therapies
- Age should not play decisive role (biologic age may)
- Close surveillance for novel toxicities:
  - 2 recent cases at Vanderbilt of rapidly fatal myocarditis after 1 dose ipi/nivo (12 and 17 days), more cases being discovered of myocarditis, rhabdomyolysis
  - 1 patient survived with steroids and early infliximab therapy (Dr. Hamid, personal communication)
  - recommending weekly CPK, Troponin x 12 weeks of ipi/nivo (ECOG, BMS trials)
- Biomarkers in development (PDL-1, MHC Class II expression)

Talimogene laherparepvec, or T-Vec, was approved to treat patients with melanoma

Imlygic (talimogene laherparepvec)

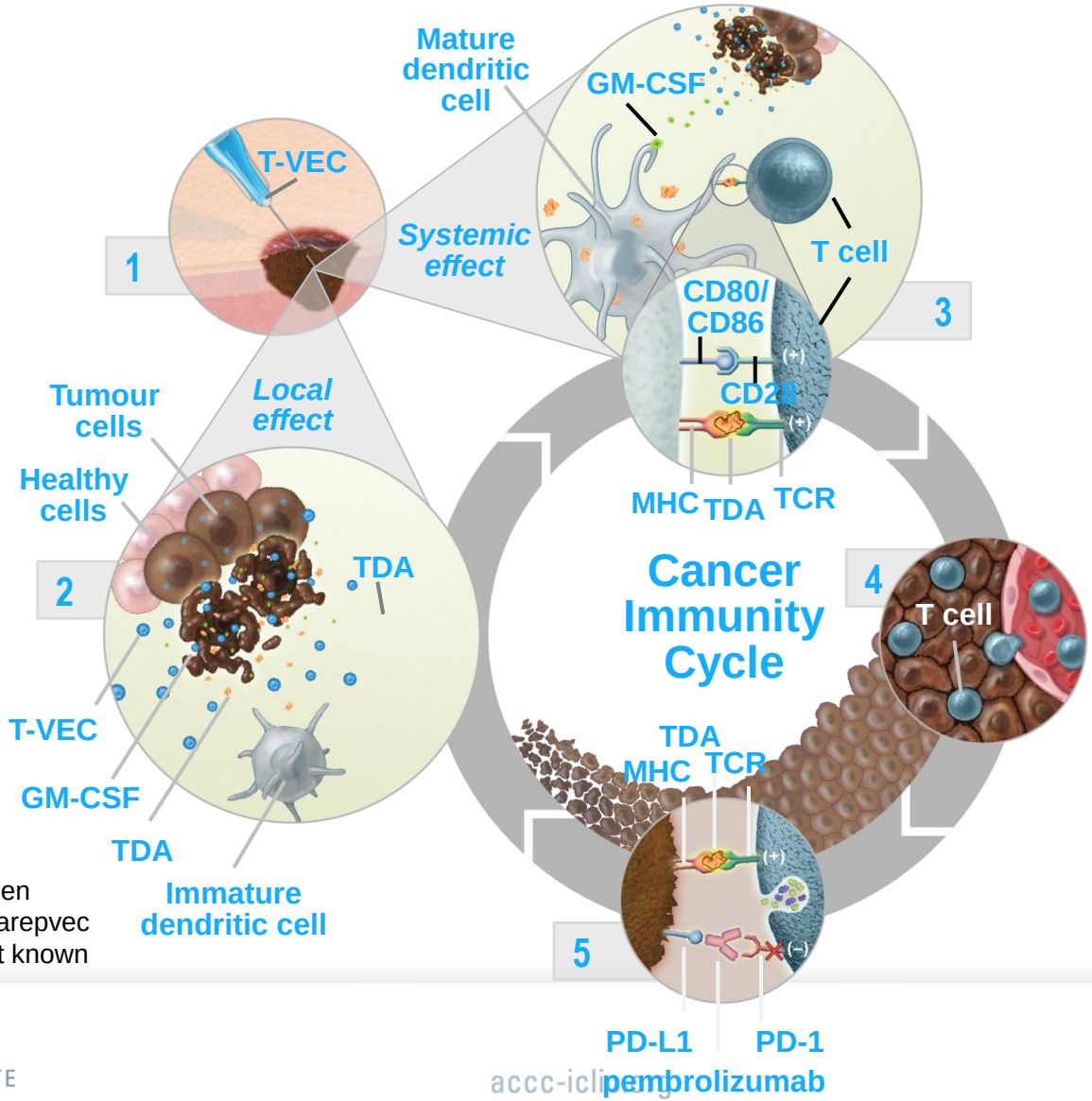
Mechanism of Action:

- T-Vec, a modified herpes virus type 1 oncolytic, replicates within tumors and produces the immune stimulatory protein GM-CSF; T-Vec causes the tumor cell to lyse releasing tumor-derived antigens which, along with GM-CSF, promotes an anti-tumor immune response

Melanoma Indication:

- Monotherapy: local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery

Proposed Mechanism of Action of T-VEC With PD-1 Inhibitor



TDA: tumour-derived antigen
T-VEC: talimogene laherparepvec
Exact MoA of T-VEC is not known

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Melanoma - T-Vec in combination with ipilimumab

***Phase Ib*, multicenter, open-label trial of T-Vec in combination with ipilimumab in patients with previously untreated, unresected stage IIIB-IV melanoma**

Dose: T-Vec administered intralesionally at ≤ 4 mL of 10^6 PFU/mL at week 1, then 10^8 Plaque Forming Units (PFU)/mL at week 4, and then once every two weeks; ipilimumab 3 mg/kg once every 3 weeks as 4 infusions starting week 6

Patients previously untreated, unresected stage IIIB-IV melanoma	T-Vec in combination with ipilimumab (n=18)
Objective Response Rate (ORR)	56% (CR = 33%)
Durable Response Rate (DRR)	44%
Median Progression-free Survival (PFS)	10.6 months
Median Overall Survival (OS)	Not reached

- 12 month and 18 month survival were 72.2% and 67%, respectively
- Grade 3 or 4 treatment-emergent adverse events = 32%; Grade 3 or 4 immune-related adverse events occurred in 2 patients; no treatment-related deaths

(source: Puzanov et al., 2015)

Melanoma - T-Vec in combination with pembrolizumab

***Phase Ib* trial of T-Vec in combination with pembrolizumab in patients with previously untreated, unresected stage IIIB-IV melanoma**

Dose: T-Vec injected into cutaneous, subcutaneous or nodal lesions at up to 4 mL of 10^6 PFU/ml day 1, then at up to 4 mL of 10^8 PFU/ml day 22 and once every 2 weeks (Q2W). Pembrolizumab is given at 200 mg IV Q2W from day 36

Patients previously untreated, unresected stage IIIB-IV melanoma	T-Vec in combination with pembrolizumab (n=16 evaluable)
Objective Response Rate (ORR)	56.3% (CR = 12.5%, PR = 43.8%)
Disease Control Rate (DCR)	68.8%

- All patients enrolled (n=21) had at least one adverse event
  - Adverse events occurring in at least 30% of patients of any grade: fatigue (52%), pyrexia (48%), chills (43%), rash (38%), headache (33%), and nausea (33%)
  - Grade 3 adverse events: headache (5%) and diarrhea (5%)
  - Treatment-related Grade 3 adverse events occurring in 5 patients: anemia, hyperglycemia, hypoglycemia, hypophosphatemia, headache, macular rash and generalized rash.
- No dose-limiting toxicities

(source: Ribas et al.., 2015; Merck Press Release, Nov. 21, 2015, http://www.mercknewsroom.com/news-release/prescription-medicine-news/merck-announces-initial-results-keytruda-pembrolizumab-novel)

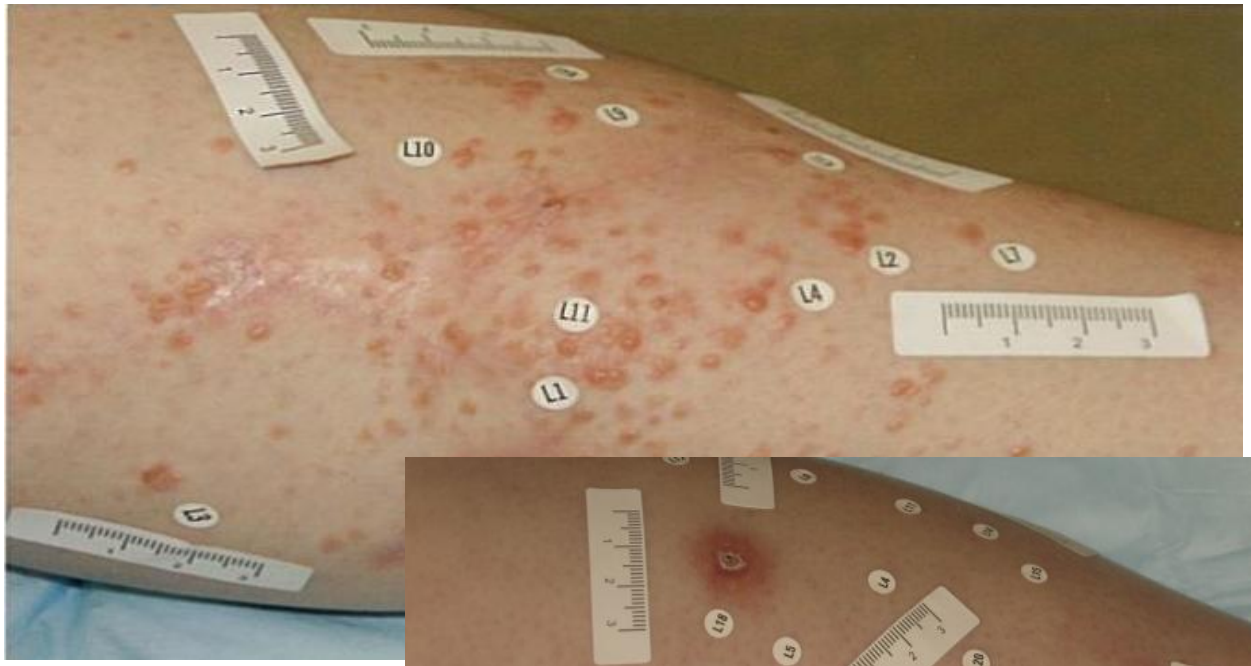
Case Report 2:

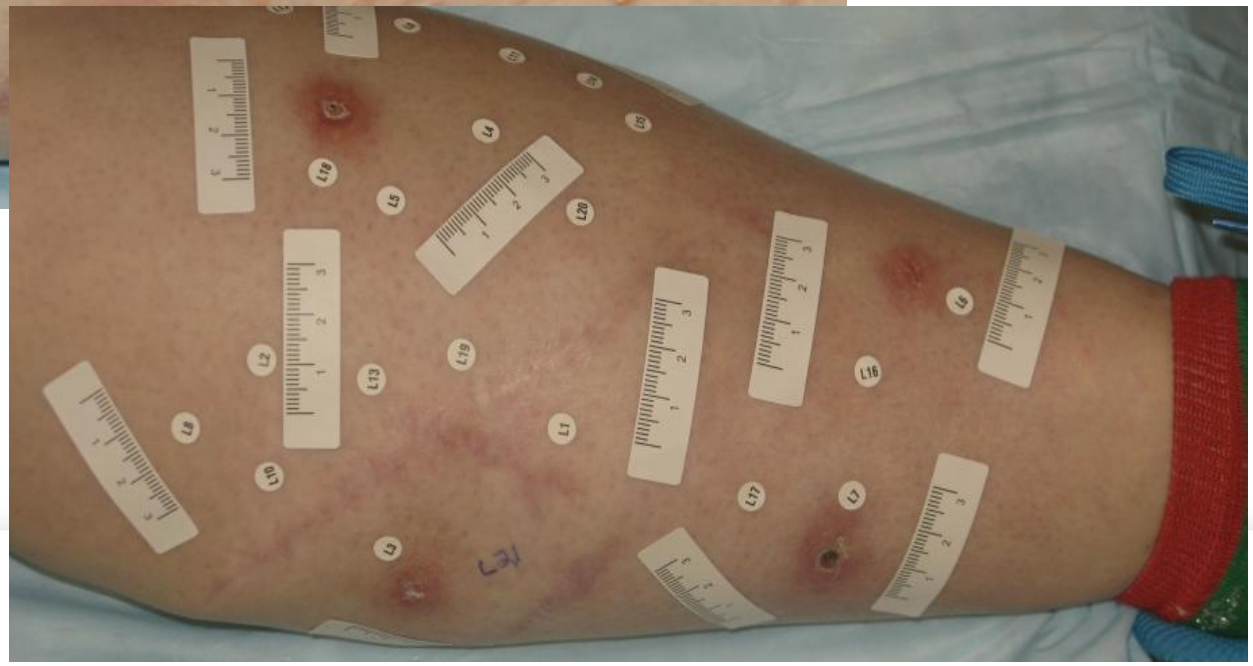
Metastatic Melanoma with Injectable Lesions

- 64-year-old white female
- Left-leg primary melanoma 06/15/12-superficial spreading melanoma pT3aN0M0, 3 mitoses/mm2
- Surveillance until
- Developed multiple in-transit metastases, lung and soft tissue distant metastases
- LDH 156 (<226)
- Stage IV, pT3aN2cM1b

T-VEC+Pembrolizumab

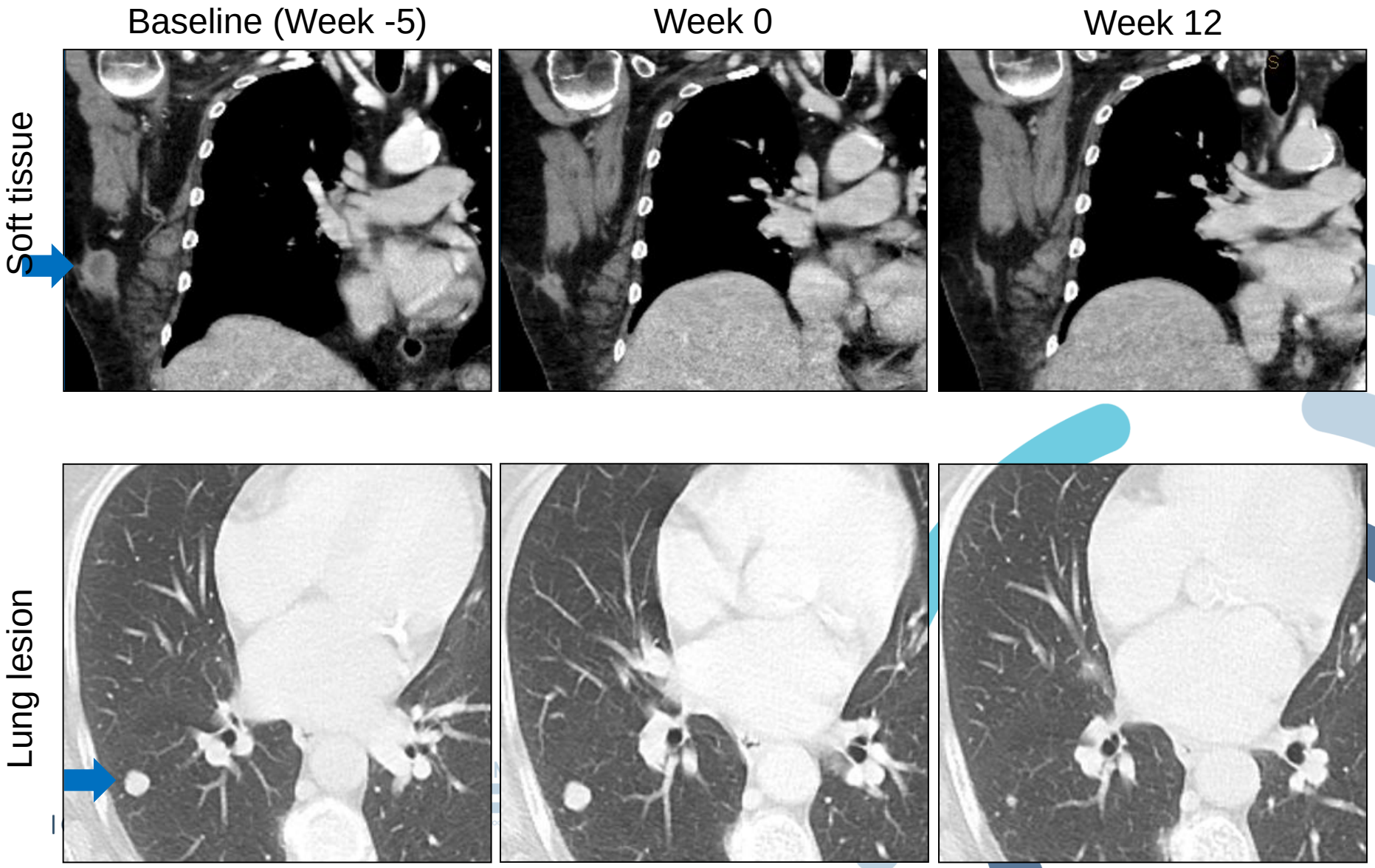
Stage IV M1b: In-Transit Lt Leg





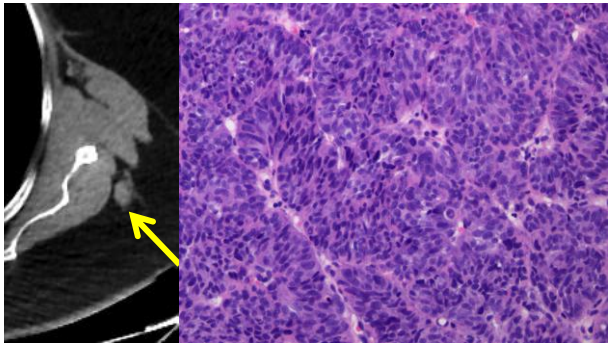
Response After 6 Weeks of Treatment

Response in Non-Injected Tumors

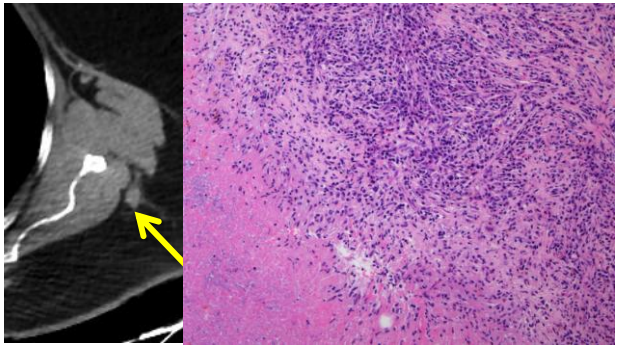


Pathological Evaluation of a persistent injected lesion

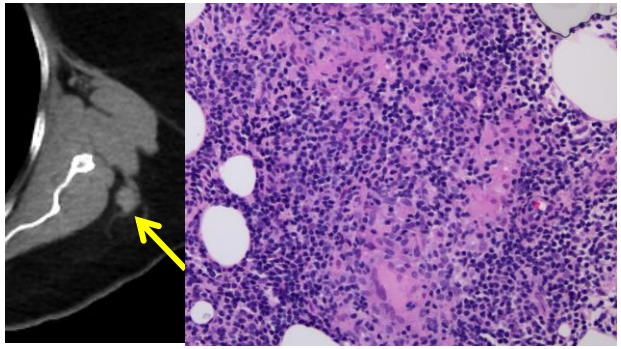
Baseline
(Week -5)



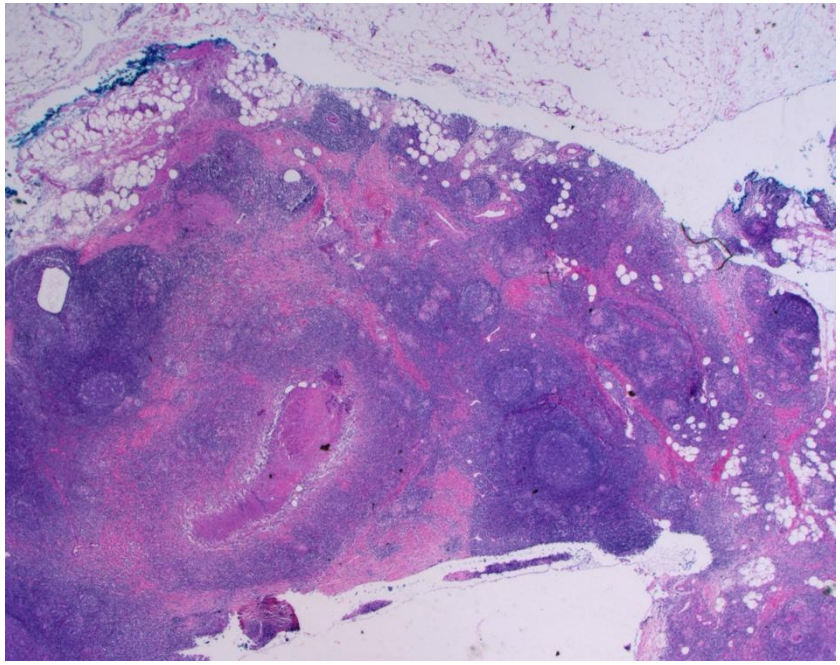
Week 0

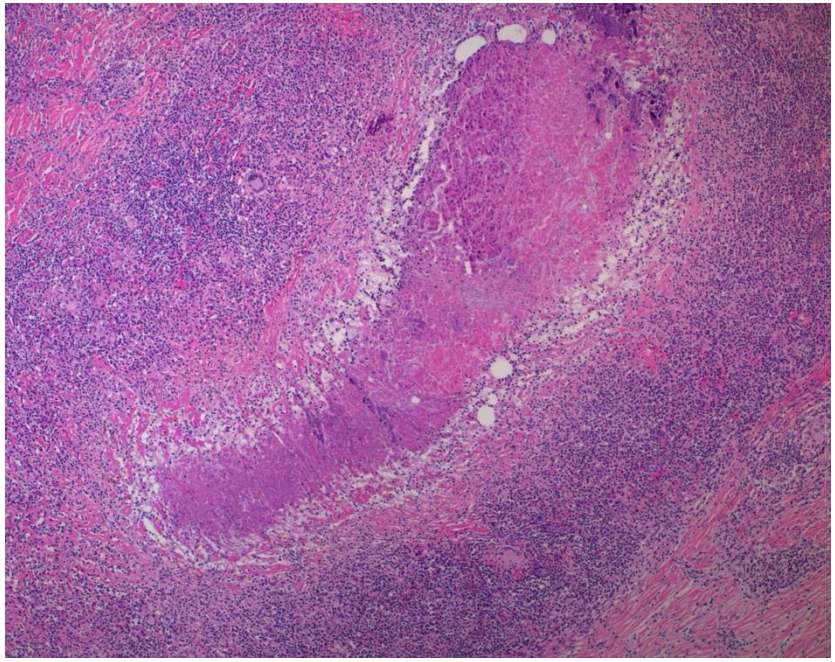


Week 24



Week 30 tumor resection





Conclusions:

Metastatic Melanoma with Injectable Lesions

- T-VEC+Ipilimumab or T-VEC+Pembrolizumab combination may be a good option for patients with injectable tumors
- Favorable toxicity profile
- Data from Phase Ib in 1st line patients
- Residual lesions may be scar tissue only
- Will need to add data or at least capture experience in pretreated patients as an addition upon progression on ipi/pembro
- Role of T-VEC injected into liver lesions currently explored for multiple tumor types (melanoma, HCC, breast, lung, gastric etc.)

Melanoma Combination Immunotherapies

Key Takeaways

- Because of their clinical effectiveness, immunotherapies are being developed in combination with each other for use in a number of tumor types
- Nivolumab in combination with ipilimumab is approved to treat patients with unresectable or metastatic melanoma
- T-Vec / ipilimumab and T-Vec / pembrolizumab are promising combination immunotherapies in development for the treatment of patients with previously untreated, unresected stage IIIB-IV melanoma

Questions?

Save-the-Date
ICLIO National Conference
September 30, 2016
Philadelphia
www.accc-iclio.org

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References

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Opdivo (nivolumab) FDA approved label, Bristol-Myers Squibb

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