ICLIO e-Course
Immunotherapy: New Mechanisms of Action

Sigrun Hallmeyer, MD

Director, Oncology Specialists
Research Institute

Oncology Specialists, SC

Chair, Cancer Committee and Medical
Director, Survivorship Program

Advocate Lutheran Hospital

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Objectives

- Review and understand the mechanisms of action of immunotherapies other than cytokines and checkpoint inhibitors in development for the treatment of cancer

- Understand the clinical evidence supporting the use of these immunotherapies in treating patients with cancer

Immunotherapy - Cytokines

Cytokines act directly on the immune system by eliciting an immune response against the tumor.

Examples of cytokines include:

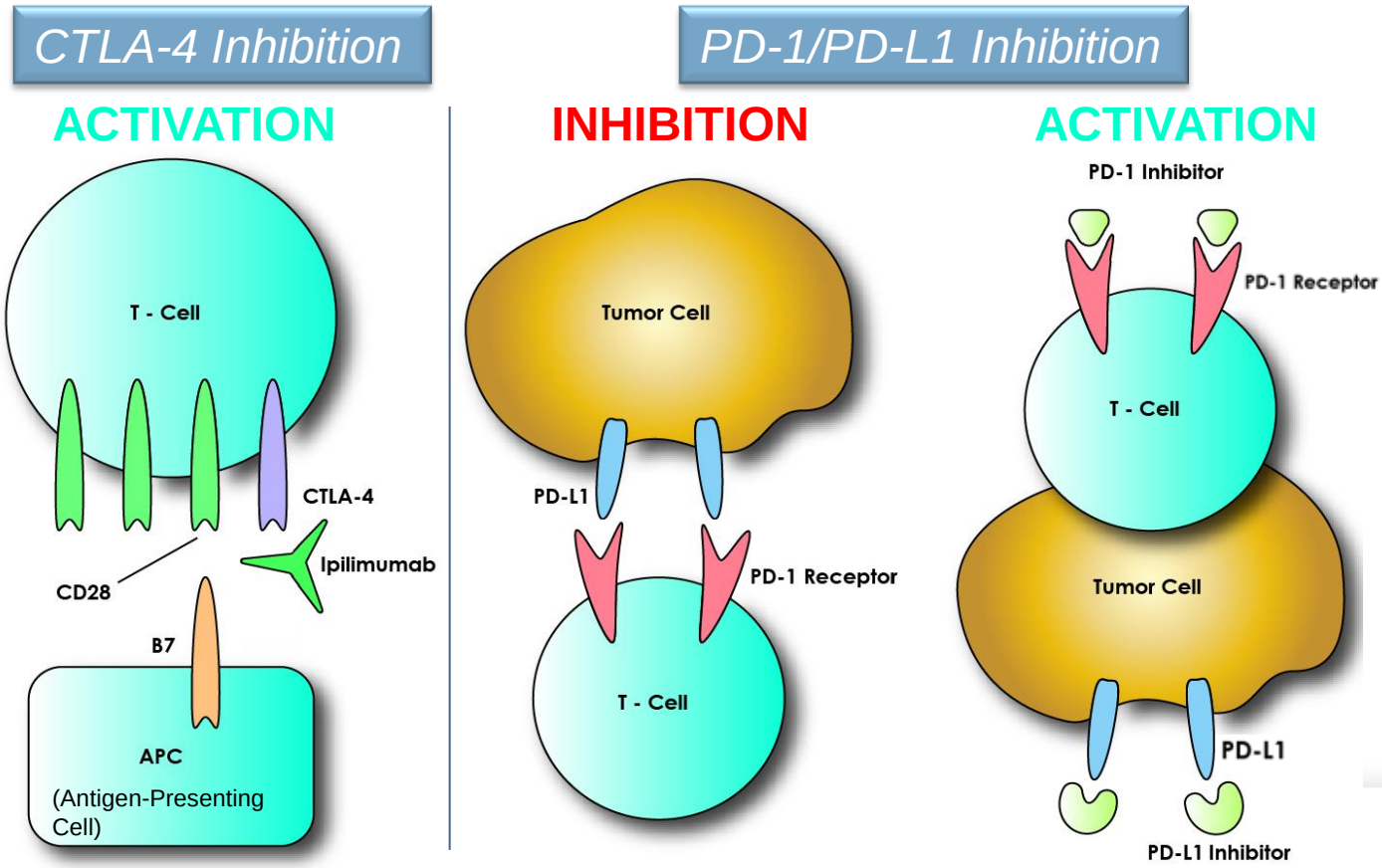
- **Interferons**: activate white blood cells such as natural killer cells and dendritic cells; peginterferon alfa-2b is an example of an interferon used to treat patients with melanoma

- **Interleukins**: increases the amount of white blood cells enhancing the immune response against cancer; aldesleukin is an example of an interleukin used to treat patients with metastatic renal cell carcinoma

(Sources: National Cancer Institute, http://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet; Cancer.Net, ASCO, http://www.cancer.net/navigating-cancer-care/how-cancer-treated/immunotherapy-and-vaccines/understanding-immunotherapy; Bristol-Myers Squibb, Immuno-Oncology, Looking Deeper into the Science of Immuno-Oncology, http://www.immunooncologyhcp.bmsinformation.com/resources/educational-resources)

Immunotherapy – Checkpoint

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



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, interferons
- Non-Small Cell Lung Cancer
  - e.g. Nivolumab, pembrolizumab
- Renal Cell Carcinoma
  - e.g. Nivolumab, interleukins

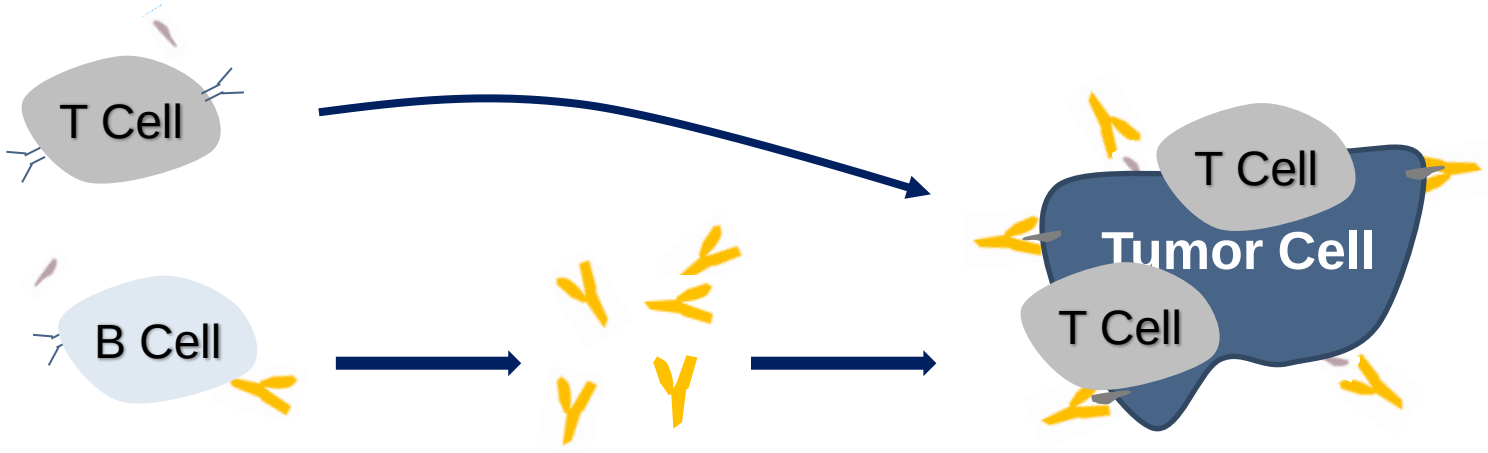
There are other immunotherapies with differing mechanisms of action

Types of Immunotherapies include:

- *Cytokines*
- *Monoclonal Antibodies*
- *Checkpoint Inhibitors*
- ***Vaccines***
- ***Cell Therapies***
- ***Oncolytic Viruses***

Immunotherapy - Vaccines

Vaccines introduce the immune system to tumor-associated antigens, inducing the immune system to recognize and attack tumor cells associated with the antigen



= tumor antigen, antigen peptides

= antibody

(sources: Bristol-Myers Squibb, Immuno-Oncology, Looking Deeper into the Science of Immuno-Oncology, http://www.immunooncologyhcp.bmsinformation.com/resources/educational-resources ; Cancer.Net, ASCO, http://www.cancer.net/navigating-cancer-care/how-cancer-treated/immunotherapy-and-vaccines/understanding-immunotherapy)

ProscaVax (PSA/IL-2/GM-CSF) Vaccine

PSA (Prostate Specific Antigens)/IL-2 (interleukin-2)/GM-CSF (granulocyte-macrophage colony-stimulating factor)

- **PSA**, produced by the prostate gland, is elevated in patients with prostate cancer; an increase in PSA levels signifies disease progression; PSA is the antigen component of this therapy
- **IL-2** increases the amount of white blood cells enhancing the immune response
- **GM-CSF** assist in the formation of white blood cells by the bone marrow and support antigen presenting cells and thus the immune system

PSA/IL-2/GM-CSF is currently in Phase Ia/Ib for the treatment of patients with recurrent prostate cancer

Two Stage Phase Ia/Ib, single-group, open-label study

- ***Eligibility***
  - Patients with recurrent prostate cancer as shown by elevated levels of PSA
  - Prior definitive therapy including surgery or radiation therapy (hormone-naïve, defined as hormone-naïve patients and patients who received hormone therapy in the past who currently have total testosterone greater than 50 ng/dL), or hormone suppressive therapy as documented by surgical castration or a serum testosterone value less than 50 ng/dL (hormone-independent) *(source: Clinicaltrials.gov, identifier NCT02058680)*
- ***Endpoints***
  - Primary endpoint: Dose Limiting Adverse Events
  - Secondary endpoints: PSA doubling times and PAP (prostatic acid phosphatase) levels; Time to measurable disease; Time to subsequent therapy; Overall Survival (OS); Vaccine-induced immune response (e.g. anti-PSA antibodies, lymphocyte activation assays, cytokine levels, etc.)

(source: Clinicaltrials.gov, identifier NCT02058680)

Initial results of PSA/IL-2/GM-CSF are promising

Phase 1a interim results:

- Patients received intradermal injections of the vaccine at Weeks 1, 2, 3, 7, 11, and 15
- 12 patients received at least one vaccination; 10 of those 12 patients were able to receive all 6 injections

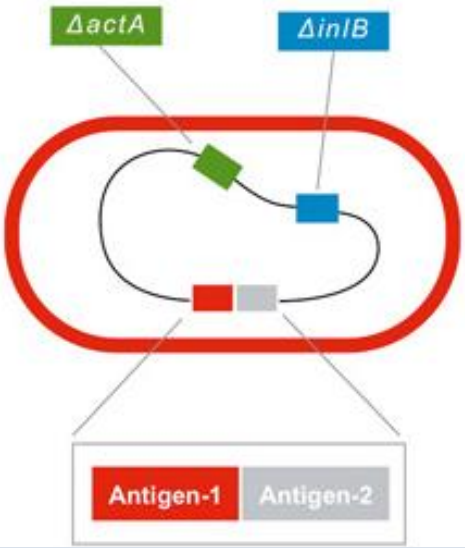
Interim Results
No dose-limiting adverse events (DLAE) for any of the patients receiving vaccinations
7 patients had increased immune responses to PSA (determined by Lymphocyte Blastogenesis Assay)

Investigators observed clinical activity, with two-thirds of patients taking the vaccine experiencing decreasing PSA levels; with no DLAEs, a Phase II trial is planned with enrollment of 120 patients

(source: Head et al, 2016; Head et al, 2015, http://oncbiomune.com/events/OBMP-CRI-Poster-2015.pdf; OncoBioMune ProscaVax Pipeline Description, http://oncbiomune.com/proscavax/)

CRS-207 is an immunotherapy vaccine in development for a number of tumor types

- CRS-207 utilizes Aduro Biotech's LADD (Live-attenuated, double-deleted Listeria monocytogenes) platform technology



(source: taken from Aduro Biotech LADD pipeline, http://www.aduro.com/pipeline/ladd/)

- LADD is an engineered, attenuated strain of the bacteria *Listeria monocytogenes;*
- LADD is genetically modified, deleting two genes, *internalin B* and *act A,* essential for the bacteria's natural ability to harmfully infect hepatocytes and spread
- LADD can be genetically manipulated to express tumor-specific antigens

CRS-207 expresses the tumor-associated antigen mesothelin, a protein which expressed in a number of different tumor types

CRS-207, in combination with GVAX Pancreas, is in Phase II for the treatment of patients with metastatic pancreatic cancer

- CRS-207, in combination with the GVAX Pancreas vaccine, resulted in improved overall survival in patients with metastatic Pancreatic Adenocarcinoma (PDA)
  - GVAX Pancreas vaccine consists of allogeneic pancreatic tumor cells genetically modified to express GM-CSF and activate specific T cell immunity to pancreatic cancer antigens, including mesothelin

Phase IIa, randomized study

Patients with metastatic PDA who received or refused ≥ 1 prior chemotherapy; median follow-up of 7.8 months	**2 doses of GVAX and low-dose cyclophosphamide (CY), followed by 4 doses of CRS-207 (n=61)**	**6 doses of GVAX and CY (n=29)**
median OS	6.1 months	3.9 months

- Median OS in patients who received ≥ 3 doses of the GVAX/CY/CRS-207 (2 doses of GVAX/CY and ≥ 1 dose CRS-207) was *9.7 months* versus *4.6 months* for those receiving ≥ 3 doses of GVAX/CY
- GVAX/CY/CRS-207 treatment was well-tolerated
- A larger, three arm, Phase IIb trial is ongoing; in addition, CRS-207/GVAX is being studied in combination with nivolumab in the STELLAR trial (Phase II) in previously treated patients with metastatic Pancreatic Adenocarcinoma

(Source: Le et al., 2014; Whiting et al., 2015; Le et al., 2015; Le et al., 2016)

CRS-207 is being studied in combination with chemotherapy for the treatment of patients with mesothelioma

- Interim results of the Phase Ib trial of CRS-207 in combination with pemetrexed/cisplatin as front-line therapy demonstrated efficacy in patients with unresectable malignant pleural mesothelioma (MPM):

Patients received 2 vaccinations with CRS-207 two weeks apart followed by up to 6 cycles of pemetrexed and cisplatin three weeks apart and 2 CRS-207 treatments 3 weeks apart

In 34 evaluable patients:

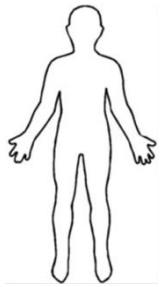
- *Disease Control Rate = 94%*
  - *59% with partial responses*
  - *35% with stable disease*
- *In 3 patients with tumor biopsies completed, biomarker analysis revealed an increase in tumor infiltrating cells (recruitment of CD8+ T-cells, dendritic cells, and natural killer cells)*
- *Median Duration of Response = 5.3 months*
- *Median Progression-Free Survival = 8.5 months*
- *No treatment-related serious adverse events or unexpected toxicities*

Final results for this trial is expected later this year; a Phase III trial of CRS-207 in combination with chemotherapy for 1st line use is being planned

(source: Aduro Biotech Press Release, 09/26/2015, Aduro Biotech Announces Phase 1b Mesothelioma Trial Featured in Spotlight Poster at ESMO/ECC, http://investors.aduro.com/phoenix.zhtml?c=242043&p=irol-newsArticle&ID=2090581)

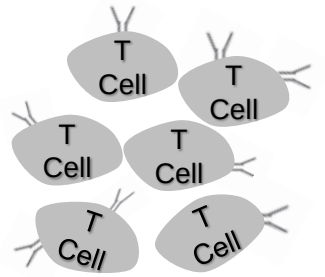
Immunotherapy – Cell Therapies

During Adoptive Cell Transfer (ACT) a patients autologous immune cells are engineered to recognize and attack the tumor cells of the patient.



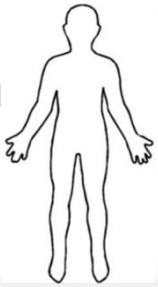
Patient's T Cells are collected from their blood

T Cells are engineered to express Chimeric Antigen Receptors (CARs) that recognize tumor antigens



T Cells are expanded and grown

T Cells are re-infused back into the patient; engineered T Cells recognize, attack, and kill the antigen-specific tumor cell



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(sources: Bristol-Myers Squibb, Immuno-Oncology, Looking Deeper into the Science of Immuno-Oncology, http://www.immunooncologyhcp.bmsinformation.com/resources/educational-resources ; National Cancer Institute, CAR T-Cell Therapy: Engineering Patients Immune Cells to Treat Their Cancers, http://www.cancer.gov/about-cancer/treatment/research/car-t-cells ; some images in this slide were taken from Powerpoint licensed Creative Commons)

CTL019 (tisagenlecleucel-T) is in Phase II for the treatment of children and young adults with relapsed/ refractory Acute Lymphomblastic Leukemia (R/R ALL)

- In CTL019 therapy, the patient's T cells are collected and genetically modified to express CARs that recognize CD19, expressed on the cell surface of tumor cells

Phase II, single-arm study, R/R ALL

- *55 out of 59 patients (93%) achieved a Complete Remission*
  - ➢ *Median follow-up of 12 months*
    - *Overall Survival at 12 months was 79%;*
    - *18 patients had ongoing Complete Remissions after 12 months*
- *88% developed Cytokine Release Syndrome (CRS) (Grade 1-4); treatment was given to 27% of patients with CRS for hemodynamic or respiratory instability and was reversed in all cases with an IL6-receptor antagonist*

❖ *FDA granted CTL019 Breakthrough Designation in pediatric and adult ALL*

❖ *CTL019 is in Phase II for other hematologic malignancies*

(source: Novartis Press Release, 12/07/2015, Novartis highlights new CTL019 Phase II data demonstrating 93% complete remission in pediatric patients with r/r ALL; Novartis Press Release, 12/06/2015, Novartis announces new CTL019 study data demonstrating overall response in adult patients with certain types of lymphoma; Grupp et al., 2015)

LN-144 is in Phase II for the treatment of patients with metastatic melanoma

- LN-144 are tumor infiltrating lymphocytes (TIL) taken directly from the patient's tumor and expanded to several billion; a tumor sample is resected from each patient and the sample is cultured with IL-2 *in vitro* to expand the population of TIL; after lymphodepletion, patients are reinfused with the autologous TIL followed by IL-2 *(source: clinicaltrials.gov, NCT02360579)*

Patients with at least one prior systemic treatment for metastatic melanoma, median follow-up was ~35 months	**LN-144 (TIL followed by IL-2) (n=101)**
Overall Response Rate	54%
Complete Response	24% (of these, 96% showed durability of response at 30 to 47 months following treatment
Overall Survival (OS)	80% at 12 months, median OS not yet achieved
Median Progression-Free Survival (PFS)	10 months, 34% were without disease progression at 4 years

Treatment with LN-144 is associated with high, durable objective response rates

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(source: Lion Biotech Press Release, 09/16/2015, Lion Biotechnologies Announces Positive Updated Data from NCI's Phase 2 Study of TIL Therapy in the Treatment of Metastatic Melanoma; clinicaltrials.gov, NCT02360579)

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

FDA approved Indication: local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery

Approval for T-VEC was based on results of a Phase III study in advanced Melanoma

- Phase III, randomized, open-label, T-VEC versus GM-CSF:

Patients with unresected stage IIIB to IV melanoma (n=436)	**T-VEC (n=295) administered intralesionally at an initial concentration of 10^6 PFU per mL Day 1, followed by 10^8 PFU per ml on Day 21 and every 2 weeks thereafter**	**GM-CSF (n=141) administered sub-Q in 28-day cycles (125µg/m^2 daily for 14 days followed by 14 days without GM-CSF)**
Durable Response Rate (DRR)	16.3%	2.1%
Overall Response Rate (ORR)	26.4%	5.7%

- Median Overall Survival was 23.3 months in the T-VEC arm, compared to 18.9 months with GM-CSF (*P*= .051)
- The most common adverse events (AEs) with T-VEC were fatigue, chills, and pyrexia; Grade 3 or 4 AEs in ≥ 2% was cellulitis at 2.1%; no fatal treatment-related AEs

T-VEC is also being studied in combination with checkpoint inhibitors for the treatment of patients with previously untreated, unresected stage IIIB-IV melanoma

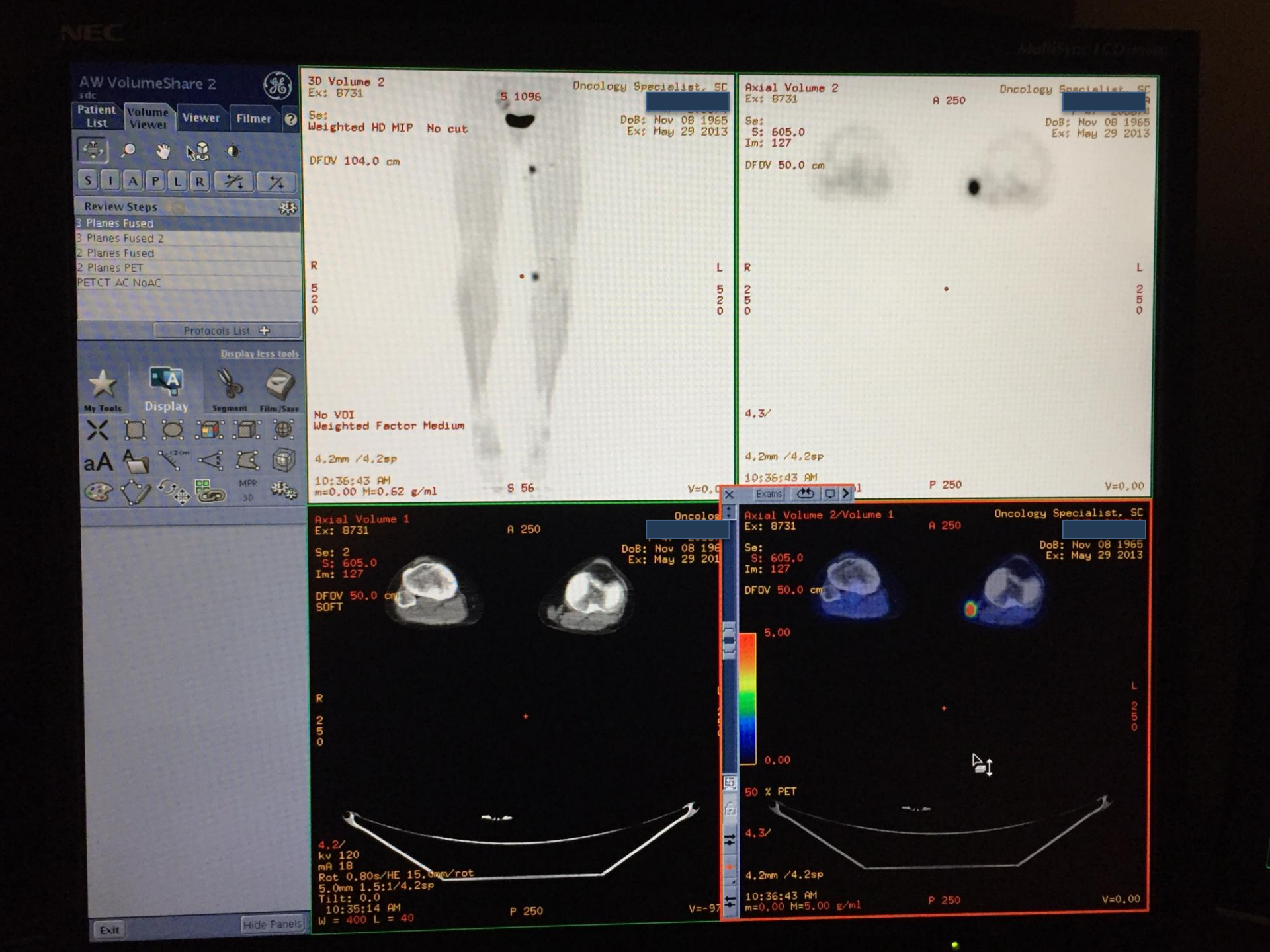
(source: Imlygic (talimogene laherparepvcec) FDA Approved Label, Amgen; Andtbacka and Kaufman et al, 2015))

Case Study Cavatak - Viralytics

- Coxsackievirus A21 is a naturally occurring virus responsible for mild upper respiratory tract infections
- Also has potent oncolytic activity
- CAVATAK is injected intra-tumor (IT) and induces lysis of tumor cells, exposing the host immune system to extra- and intracellular tumor specific antigens

Patient Case Study

- 48 y/o female with T4b (5.1mm, ulcerated) nodular melanoma left first hallux
- Underwent WLE and SLNB (neg)
- 4 months later developed sc nodule on leg, excision performed (in-tansit)
- 6 weeks later multiple new in-transit lesions on leg – unresectable stage III
- Receives 2 cycles ipilimumab, presenting with new omental caking and abdominal pain – omental biopsy + for melanoma, stage IV disease
- Receives 1 course high dose IL2 (15/24 doses), CT shows resolution of abdominal disease but lower extremity lesions unchanged
- Receives 2 additional doses ipilimumab – disease progression in leg
- Starts injections with CAVATAK IT over 4 months – achieves CR
- Has maintained CR since October 2013 (28+ months)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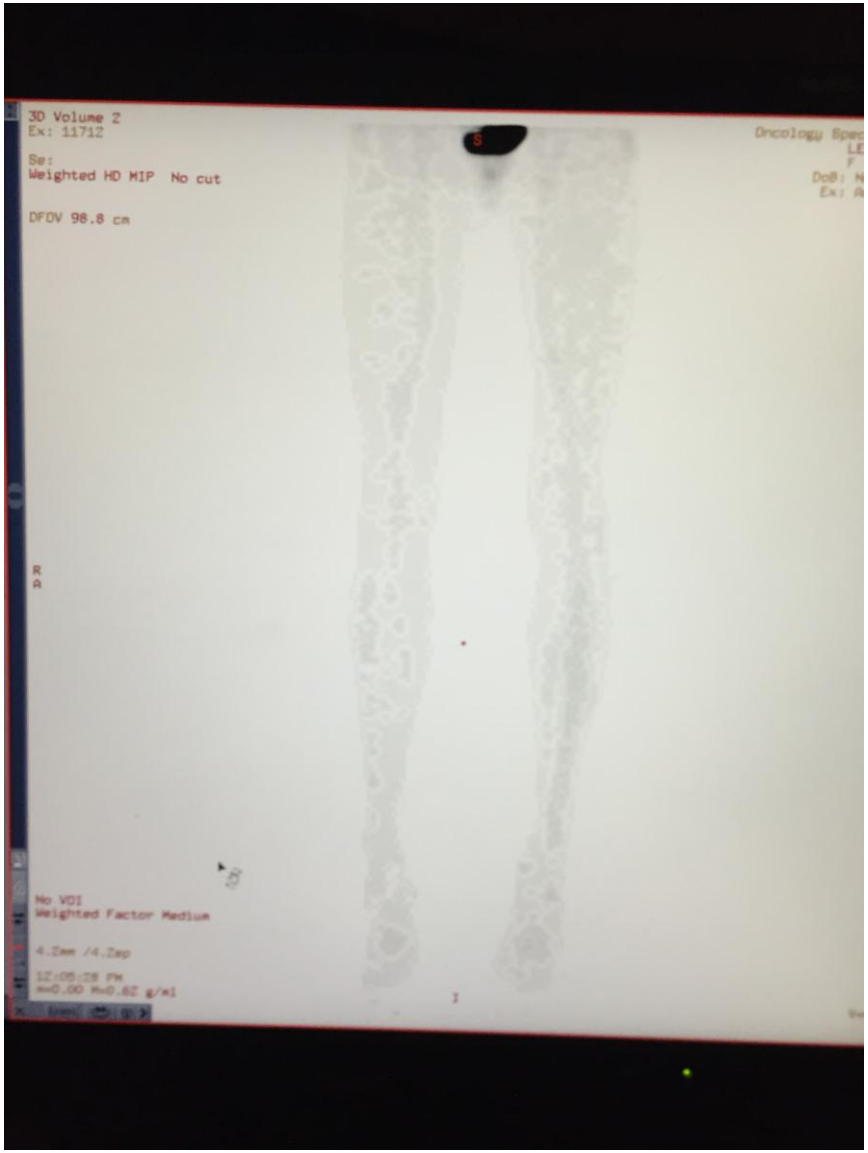
- First PET scan after resolution of palpable/injectable lesions have become no longer measurable
- Maintained PET and exam negative status for 28+ months, ongoing



New Mechanisms of Action

Key Takeaways

- **In the future, there will be a number of immunotherapies in addition to cytokines and checkpoint inhibitors that will be available to treat patients with cancer, including:**
  - **Vaccines: Vaccines introduce the immune system to tumor-associated antigens, inducing the immune system to recognize and attack tumor cells associated with the antigen; ProscaVax and CRS-207 are examples of immunotherapy vaccines currently in development**
  - **Cell Therapies: Cell therapies in development include CTL019 and LN-144; these therapies utilize a patient's autologous immune cells which are engineered to recognize and attack the patient's tumor cells**

- **Oncolytic viruses are a type of immunotherapy indicated for the treatment of melanoma**
  - **T-Vec is approved for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery; T-VEC is being studied in combination with checkpoint inhibitors for the treatment of patients with previously untreated, unresected stage IIIB-IV melanoma**

Questions?

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Imlygic (talimogene laherparepvcec) FDA Approved Label, Amgen

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