ICLIO e-Course
Immunotherapy: New Mechanisms of Action

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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.

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.

**CTLA-4 Inhibition**

**ACTIVATION**

- T-Cell
- CTLA-4
- CD28
- Ipilimumab
- B7
- APC (Antigen-Presenting Cell)

**PD-1/PD-L1 Inhibition**

**INHIBITION**

- Tumor Cell
- PD-L1
- PD-1 Inhibitor
- PD-1 Receptor

**ACTIVATION**

- T-Cell
- PD-L1
- PD-1 Receptor
- PD-L1 Inhibitor
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.

\[ \text{T Cell} \rightarrow \text{B Cell} \rightarrow \text{Tumor Cell} \]

- = tumor antigen, antigen peptides

\[ \text{\downarrow} = \text{antibody} \]

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

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**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)

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*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*

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

  - 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**

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

During Adoptive Cell Transfer (ACT) a patient’s 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

(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 Lymphoblastic 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 \textit{in vitro} to expand the population of TIL; after lymphodepletion, patients are reinfused with the autologous TIL followed by IL-2 \textit{(source: clinicaltrials.gov, NCT02360579)}

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<th>Patients with at least one prior systemic treatment for metastatic melanoma, median follow-up was ~35 months</th>
<th>LN-144 (TIL followed by IL-2) (n=101)</th>
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<tr>
<td>Overall Response Rate</td>
<td>54%</td>
</tr>
<tr>
<td>Complete Response</td>
<td>24% (of these, 96% showed durability of response at 30 to 47 months following treatment)</td>
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<tr>
<td>Overall Survival (OS)</td>
<td>80% at 12 months, median OS not yet achieved</td>
</tr>
<tr>
<td>Median Progression-Free Survival (PFS)</td>
<td>10 months, 34% were without disease progression at 4 years</td>
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\textbf{Treatment with LN-144 is associated with high, durable objective response rates}

\textit{(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:

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<th>Patients with unresected stage IIIB to IV melanoma (n=436)</th>
<th>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</th>
<th>GM-CSF (n=141) administered sub-Q in 28-day cycles (125μg/m² daily for 14 days followed by 14 days without GM-CSF)</th>
</tr>
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<tbody>
<tr>
<td>Durable Response Rate (DRR)</td>
<td>16.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Overall Response Rate (ORR)</td>
<td>26.4%</td>
<td>5.7%</td>
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- 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 $\geq 2\%$ 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 laherparepvec) 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-transit)
- 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)
• 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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Thank You

Save-the-Date
ICLIO National Conference
September 30, 2016
Philadelphia

www.accc-iclilo.org
References


Bristol-Myers Squibb, Immuno-Oncology, Looking Deeper into the Science of Immuno-Oncology, http://www.immunooncologyhcp.bmsinformation.com/resources/educational-resources


Clinicaltrials.gov, identifier NCT02058680

Clinicaltrials.gov, identifier NCT02360579


Imlygic (talimogene laherparepvec) FDA Approved Label, Amgen
Le, D.T. et al. Randomized phase II study of the safety, efficacy, and immune response of GVAX pancreas (with cyclophosphamide) and CRS-207 with or without nivolumab in patients with previously treated metastatic pancreatic adenocarcinoma (STELLAR). *J Clin Oncol* 34, 2016 (suppl 4S; abstr TPS486)


