Science Webinar Series
Part 5: Targeting cancer pathways: Understanding immune checkpoints
January 19, 2016

Participating experts

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Immune Checkpoint Blockade in Cancer Therapy: New insights, opportunities, and prospects for cures

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Thanks to:

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Dana Leach
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Tsvetlina Pentcheva

**Also:**

Medarex
Bristol Myers-Squibb
The Docs
The Patients

**Funding:**

NCI
HHMI
Ludwig Trust
MRA
CPRIT
SU2C/CRI
FDA approval of antibodies targeting immune checkpoints

- 2011 Ipilimumab (BMS) - Melanoma
- 2014 Pembrolizimab (Merck) – Melanoma
- 2014 Nivolumab (BMS) – Melanoma
- 2015 Nivolumab (BMS) – Lung
- 2015 Ipilimumab + Nivolumab (BMS) – Melanoma
- 2015 Pembrolizumab (Merck) – Lung
- 2015 Ipilimumab (BMS) – Adjuvant melanoma
- 2015 Nivolumab (BMS) – Renal cell carcinoma
Immune Checkpoint Blockade

Paradigm Shift in Cancer Therapy:

*Doesn’t target tumor cells*

*Doesn’t involve vaccines or cytokines to turn “on” immune responses*

*Works by blocking inhibitory pathways to unleash anti-tumor immune responses*
How did we get here?

Understanding of fundamental mechanisms of T cell activation and regulation
Dynamic Integration of TCR and Costimulatory Signals

*circa 1996*

**No Proliferation Anergy?**

- T Cell
- APC
- TCR
- CD28
- Peptide/MHC
- B7-1,2
- pRb
- Cdk6
- Cdk4
- Cyclin D1
- Cyclin D2
- p27kip

**Activation, Initiation**

- IL-2
- S phase
- Bcl-xL,γ
- Cdk6
- Cdk4
- Cyclin D1
- Cyclin D2

**Inhibition**

- IL-2
- pRb
- Cdk6
- Cdk4
- Cyclin D1
- Cyclin D2

**Restricted Proliferation**

Gross, Harding, Krummel, Chambers, Brunner, Egen, Kuhns
CTLA-4 Blockade Enhances Tumor-Specific Immune Responses

Attenuated or Terminated Proliferation

Unrestrained Proliferation

Necrotic Death
Vaccines
Chemotherapy
Irradiation
Hormone therapy
Anti-angiogenesis
Antibodies
“Targeted” Therapies

TCR
CD28
CTLA-4
Peptide/MHC
B7-1,2
Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma

Average Tumor Size (mm²)

Days After Tumor Injection

0 3 6 9 12 15 18 21 24 27 30 33 35 38

Anti-CD28
No Rx
Anti-CTLA-4

Leach
Anti-CTLA-4 and GM-CSF Tumor Cell Vaccine Synergize to Eradicate Established B16 Melanoma

Days After Tumor Injection

Average Tumor Size (mm$^2$)

No Rx

GM-Vaccine

Anti-CTLA-4

Both

van Elsas, Hurwitz
Anti-CTLA-4/GVAX therapy activates the tumor vasculature and increases infiltration of tumors by CD4 and CD8 effector cells.
Anti-CTLA-4/GVAX therapy activates the tumor vasculature and increases infiltration of tumors by CD4 and CD8 effector cells

Untreated

αCTLA-4/GVAX

Quezada
Ipilimumab
(Medarex, Bristol-Myers Squibb)

Fully human antibody to CTLA-4

>50,000 patients treated to date:

Objective responses in many tumor types, including melanoma, prostate, kidney, bladder, ovarian & lung cancer, etc.

Adverse events (colitis, hepatitis, hypophysitis, etc.) serious but generally manageable
The longest survivor on ipilimumab?

May 2001, after progression on IL-2

10 years later

Baseline and post-MDX-010 treatment CT scans of patient with metastatic melanoma (status post dendritic cell vaccine) who experienced regression of all known sites of disease. The patient continues without relapse at last reported follow-up visit.

Ribas
Ipilimumab in Metastatic Melanoma: Pooled OS Analysis Including EAP Data (4846 Patients)

Median OS (95% CI): 9.5 (9.0–10.0)

3-year OS Rate (95% CI): 21% (20–22%)

Hodi, ECCO 2014
Programmed Death 1

http://www.melanoma.org/community/mpip-melanoma-patients-information-page/video-how-anti-pd-1-therapy-works-immune-system
Anti – PD-1 (BMS-936558)

296 Patients with Metastatic Cancer
1, 3, 10 mg/kg, MTD not reached

Safety: Adverse events similar to Ipilimumab, but 4% pneumonitis (3 deaths)

Clinical Activity:
Melamona (n= 94): 28% CR/PR, 6% SD
NSCLC (n=76): 18% CR/PR, 7% SD
RCC (n= 33): 27% CR/PR, 27% SD
CRC (n=19), CRPC (n=13): No responses

Topalian ASCO, NEJM 2012
Overall Survival: Nivolumab (αPD-1) in Metastatic Melanoma

Topalian et al. JCO 2014
<table>
<thead>
<tr>
<th></th>
<th>Anti-CTLA-4</th>
<th>Anti-PD-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hard wired</td>
<td>• Hard wired</td>
<td>• Induced resistance</td>
</tr>
<tr>
<td>Targets CD28 pathway</td>
<td>• Targets CD28 pathway</td>
<td>• Targets TCR pathway</td>
</tr>
<tr>
<td>Expands clonal diversity</td>
<td>• Expands clonal diversity</td>
<td>• Does not expand clonal diversity</td>
</tr>
<tr>
<td>Can move T cells into tumor</td>
<td>• Can move T cells into tumor</td>
<td>• Does not move T cells into tumors</td>
</tr>
<tr>
<td>Disease recurrence after response is rare</td>
<td>• Disease recurrence after response is rare</td>
<td>• Disease recurrence after response is significant</td>
</tr>
</tbody>
</table>
Where do we go from here?

Combinations
Clinical Activity in Melanoma Patients Receiving Ipilimumab (αCTLA-4) and Nivolumab (αPD-1)

65% Clinical Activity

~50% Objective CR+PR

ASCO 2013
NEJM 6/2/2013
Prevalence of somatic mutations in human cancer

Signatures of mutational processes in human cancer Alexandrov et al.
Potential characteristics of immunogenic and nonimmunogenic tumors

**A**
- CD8 T cell
- CD4 T cell
- Tumor cell with PD-L1 expression
- CD8 T cell with PD-L1 expression
- CD8 T cell with granzyme B

**B**
- Nonimmunogenic tumor microenvironment
  - Combination therapies with agents that create immunogenic tumor microenvironment and immune checkpoint therapy

Immunogenic tumor microenvironment
- Immune checkpoint therapy and durable clinical benefit

Durable clinical benefit

Padmanee Sharma, and James P. Allison Science
2015;348:56-61

Published by AAAS
Infiltrates in Prostate Cancer: Pre- and Post αCTLA-4 therapy

Pretreatment

Post anti-CTLA-4
Infiltrates in Prostate Cancer: Pre- and Post αCTLA-4 therapy

PDL1 is expressed on CD8 cells
Combinations to enhance immune checkpoint targeting resulting in CURE

- Blocking multiple checkpoints (negative and positive)
- Conventional therapies
- Blocking other immunosuppressive factors
  - Local ablation
  - Enhancing innate immunity
- Vaccines, shared and individual
- Genomically targeted therapies
Improving Survival with Combination Therapy

% Survival

Time

Control
Standard or Other Therapy
Improving Survival with Combination Therapy

- Control
- Standard or Other Therapy
- Immunotherapy (anti-CTLA4)
Improving Survival with Combination Therapy

Control
Standard or Other Therapy
Immunotherapy (anti-CTLA4)
Combination

% Survival vs Time
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Cambridge, MA
PD-1 Cancer Immunotherapy
Gordon Freeman, PhD
Professor, Department of Medical Oncology
Immunology has offered hope for curing cancer for 100 years

What is different now?

New Strategy
Blockade of pathways used by tumors to inhibit anti-tumor immunity

Checkpoint blockade
T cells are white blood cells that can kill cancer cells: more is better.

1000 T cells  18 divisions (6 days)  millions of T cells
T cells need 2 signals for activation

- There are positive and negative second signals
The PD-1 Pathway Inhibits T Cell Activation

Dephosphorylation

Proximal signaling kinases

Reduced TCR signaling
Reduced cytokine production
Reduced target cell lysis
Altered lymphocyte motility
Metabolic programming

ITSM
SHP-2
ITIM

ITIM
PD-1
PD-1 ligand

PD-L1 (B7-H1)
PD-L2 (B7-DC)

APC

TCR
CD3
CD8

MHC

CTLA4
B7-1
Why have negative signals like PD-1?

1. Tune down the immune response after elimination of disease

2. Prevent too strong an immune response damaging tissues

3. Maintain immune tolerance
PD-L2 is a second ligand for PD-1 and inhibits T cell activation

Discovery may shed light on cancer’s shield against the immune system

For years, a question has tantalized cancer researchers: why is the immune system, normally so adept at unmasking and eliminating foreign invaders and abnormal cells, not always spry enough to destroy tumor cells?

A new study by Dana-Farber scientists suggests an answer.

In a paper published in the March issue of Nature Immunology, investigators led by Gordon Freeman, Ph.D., of Adult Oncology report that a structure
PD-L1 on tumors

- Expressed on cell surface of ~30% of solid tumors and selected hematologic malignancies
- Inhibits anti-tumor immune responses

Kidney cancer

Brown = PD-L1

Signoretti, Rodig, Atkins, McDermott; BWH, BIDMC, & DFCI
PD-1 or PD-L1 Blockade allows reactivation of anti-tumor T cell responses.

Increased cytokines

**IFN-γ**

antibody drug

Increased killing

**Tumor cell**

**CD8+ CTL**

**PD-1**

**PD-L1**

**TCR**

**MHC**
Pharmaceutical companies have developed Antibody Drugs

• Anti-PD-1 antibody
  – Nivolumab (Bristol Myers Squibb)
  – Pembrolizumab (Merck)
  – Pidilizumab (Curetech)
  – MEDI-0680 (AstraZeneca)
  – PDR001 (Novartis)
  – REGN2810 (Regeneron)

• Anti-PD-L1 antibody
  – Atezolizumab (MPDL3280, Roche)
  – Durvalumab (MEDI-4736 AstraZeneca)
  – Avelumab (MSB0010718C EMD Serono)
  – MDX-1105 (Bristol Myers Squibb)

Multiple other agents in development

FDA approved

FDA approved
Phase I clinical trial of anti-PD-1 antibody Nivolumab: Kidney Cancer cohort (34 patients)

- Generally tolerable: fatigue, rash, pruritus, diarrhea
  - Each line follows growth or shrinkage of tumor in one patient
  - 29% objective responses
  - All stopped therapy

![Graph showing change in tumor size over weeks since treatment initiation.](Image)
PD-1 Cancer Immunotherapy is different from chemotherapy

• Well tolerated: This is not chemotherapy or a cell poison! some nausea, no hair loss, no blood count decline.

• Good safety profile

• Most serious adverse events are autoimmune-mediated, like pneumonitis, colitis. Less than 10% of patients

• Physicians will have to learn to manage a different spectrum of adverse events than those seen in chemotherapy

• This can be community hospital medicine: half-hour intravenous drug infusion.
PD-1 is better than chemotherapy for melanoma

A Overall Survival

Hazard ratio for death, 0.42 (99.79% CI, 0.25–0.73) P<0.001

Patients Who Died
Nivolumab 50/210
Dacarbazine 96/208

Median Survival
Nivolumab Not reached
Dacarbazine 10.8 (9.3–12.1)

Broad anti-tumor efficacy of anti-PD-L1/PD-1 inhibitors: Overall Response Rates

Modified from D. Chen, BioScience Forum, 2015

243 clinical studies with 55,099 patients
What does the immune system see in a tumor to attack?
The immune system recognizes protein coding changes in the tumor cell, called tumor neoantigens.

Tumors have multiple neoantigens that T cells can attack.
Two evolutionary processes in cancer:

1. DNA mutation
   - rare driver mutations
   - many passenger mutations
2. Immune evasion: PD-L1, IDO, TGF-b, IL-10, loss of MHC, others
Why the enthusiasm for immunotherapy?

Data from Steve Hodi & ECCO

Moderate percentage but long-term

Chapman NEJM 2011

High percentage but short-term
Understanding immunology and genetics has identified groups that respond well to PD-1 / PD-L1 therapy

- Highly mutated tumors (MSI, defects in DNA repair) 62%
- Genetically amplified PD-L1 and PD-L2 (Hodgkin) 87%
- With Viral antigens (HPV, Head and neck, Merkel)
- What other cancer types might respond well ??
Exhausted Tumor infiltrating lymphocytes express multiple immunoinhibitory receptors:

These are druggable targets for tumor immunotherapy
The Future is Combination Therapy

- **PD blockade + other immunoinhibitor blockade:**
  *CTLA-4, TIM-3, LAG3, TIGIT, CD244, CD160*

- **PD blockade + immunostimulators:**
  *anti-OX40, anti-CD137, ICOS, IL-2, TLR ligands*

- **PD blockade + kinase inhibitors:**
  *Braf inhibitor, etc*

- **PD blockade + others:**
  *Angiogenesis blockade, radiation, HDAC inhibitors*

- **PD blockade + cancer vaccine, oncolytic virus, CAR-T**
To be done

• How do we identify who will respond to PD-1 blockade?

• What are mechanisms of failure to respond?
  – Other immunoinhibitors?
  – Failure of immune cells to infiltrate tumor?
  – No good neoantigens?

◆ How do we afford this expensive treatment: about $150,000?
It’s a great time to be an oncologist or researcher

• PD-1/PD-L1 works on a wide range of tumors with
  – moderate percentage of responders
  – good safety profile

• PD-1/PD-L1 gives us a foundation to build on

• With this success, human creativity has been unleashed and we’re learning to do better
Dana-Farber Cancer Institute

- Yanping Xiao
- Kathleen Mahoney
- Sanhong Yu
- Sarah Klein
- Xia Bu
- Apoorvi Chaudhri

- Ping Hua
- Baogong Zhu
- Yahui Hao
- Daniel Baumann
- Lilly Cai
- Ed Greenfield
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Harvard Medical School
- Arlene Sharpe

Beth Israel Deaconess Medical Center
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- Sabina Signoretti
- Scott Rodig

U of Pennsylvania
- Jaikumar Duraiswamy
- George Coukos
- E. John Wherry

Emory University
- Rafi Ahmed

Kyoto University
- Tasuku Honjo

Genetics Institute
- Clive Wood
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Cambridge, MA
Therapeutic Targeting of the Immune System to Treat Cancer

Philip Gotwals

Executive Director, Exploratory Immuno-Oncology
Novartis Institutes for Biomedical Research
CTLA-4 and PD-1 pathway therapies are transformative, but there remains room for improvement

- Despite the great clinical success of antagonist antibodies to CTLA-4, PD-1 and PD-L1:
  - Response rates range from 10-40%
  - Resistance/relapse remain
  - Patients without a pre-existing anti-tumor immune response appear not to benefit from these therapies
  - Patient selection strategies remain unclear
Multiple emerging strategies target the immune system and combinations will be critical

- Combining checkpoint inhibitors and targeted therapies
- T cell targeting/novel checkpoint inhibitors
- Targeting the immunosuppressive tumor microenvironment
- Engineered T cell therapy
- Immune priming
Targeted and immuno-modulatory therapeutics are being combined in melanoma

- Phase 1 study combining anti-PD-L1 (MEDI4736) with BRAF (dabrafenib and/or MEK (trametinib) inhibitors in advanced melanoma. Ribas et al 2015 ASCO Annual Meeting (3003)
Therapeutic Immuno-oncology Approaches
Selected Examples from Industry and the Novartis Immuno-oncology Portfolio

Immune boosting

T-cell modulation
- PD1/PDL1
- LAG-3
- CART therapy

Tumor microenvironment

**Dendritic cells**
- Antigen uptake & processing
- Dendritic cell maturation
- Tumor antigen

**Antigen presentation**

**Cytotoxic T-cell responses**

**Effector T-cell**

**T-cell activation**

**Tumor**

**Lymph node**
- Antigen presentation
- T-cell activation

**Regulatory T-cell responses**

**NK cell**

**PD-1 receptor**

**Regulatory T-cell suppression**

**Immunosuppression**
A wealth of important targets for T cell modulation

In addition to antigen specific recognition signals, T cells receive positive and negative second signals from APCs.

Costimulatory signals regulate the responsiveness of many immune cells including naïve, effector, memory & regulatory T cells and B cells.

Co-inhibitory signals in natural settings promote tolerance but can cause T cell exhaustion in pathologies having a chronic presence of an antigen (viral exhaustion) and in cancer.
LAG-3

**Lymphocyte activation gene-3**

- LAG-3 is expressed across a number of activated T-cells and dendritic cells, and is frequently co-expressed with PD-1 on anergic or exhausted T-cells\(^1\)\(^-\)\(^3\)
- Known ligands include MHC Class II, L-SECTin, and galectin-3\(^2\)\(^,\)\(^3\)
- LAG-3 negatively regulates T-cell signaling and function in effector T-cells by binding MHC class II molecules, and supports the suppressive phenotype of regulatory T-cells\(^1\)\(^-\)\(^3\)
- Blockade restores activity of Teffs, diminishes suppressor activity of natural Tregs and Type 1 regulatory T cells, and enhances anti-PD-1 antitumor activity\(^3\)
- Combined inhibition of LAG-3 and PD-1 may be more efficacious in inducing tumor regression\(^3\)

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MHC, major histocompatibility complex.

LAG525
A LAG-3 Receptor-targeting Monoclonal Antibody

- LAG525 is an immunoglobulin G4 humanized monoclonal antibody that binds LAG-3 with low nanomolar affinity, inhibiting LAG-3 interaction with MHC class II molecules
  - LAG525 was stable, with slow clearance and a mean half-life of 10.6 days in nude mice
- The clinical program for LAG525 will explore whether LAG-3 blockade restores activity of antitumor effector cells and enhances anti-PD-1 antitumor activity, as a monotherapy, and in combination with anti-PD-1 therapy

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Treatment/Setting</th>
<th>Phase</th>
<th>N</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02460224</td>
<td>Advanced/metastatic solid tumors, including NSCLC, melanoma, renal cancer, gastric cancer, esophageal adenocarcinoma, nasopharyngeal cancer, and CRC</td>
<td>1/2</td>
<td>≈240</td>
<td>Part 1: DLTs Part 2: ORR</td>
</tr>
</tbody>
</table>

Chimeric Antigen Receptor (CAR) T Cells – Engineering T cells to directly attack tumors

Immune cells from patient → Viral vector → Re-engineer to target cancer → CART-19 → Re-inject into patient → Cell killing

Cancer Cell → CD19
## CTL019 Therapy: Overview of Recent Clinical Data in Hematologic Malignancies

<table>
<thead>
<tr>
<th>Disease State (R/R)</th>
<th>Complete Response</th>
<th>Other Response Parameters</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ped. ALL</td>
<td>92% (36/39)</td>
<td>6 month duration of response 76%</td>
<td>All pts. Developed CRS; 37% required tocilizumab + steroids</td>
</tr>
<tr>
<td>CLL</td>
<td>21% (5/24)</td>
<td>42% ORR (10/24)</td>
<td>31% had grade 2-4 CRS</td>
</tr>
<tr>
<td>NHL (DLBCL, FL)</td>
<td>25% (5/20)</td>
<td>65% ORR (13/20)</td>
<td>Grade &gt;3 CRS occurred in 9% of total pts.</td>
</tr>
</tbody>
</table>

Reported at ASH 2014, AACR 2015, and ASCO 2015
ORR: Overall Response Rate; CRS – Cytokine Release Syndrome
Expanding the CART Platform beyond CD19+ tumors

Examples of New Targets

- **EGFRvIII:**
  - CAR therapy for Glioblastoma Multiform
  - FPFV achieved in January 2015
  - Early data presented at ASCGT in May 2015

- **BCMA:**
  - CAR therapy for Multiple Myeloma
  - FPFV achieved in November 2015

Next Generation

- Pharmacological Control of CART activity
  - Multiple strategies to regulate CART function or remove the CART cells

- Gene Editing using CRISPR technology
  - Allogeneic or “off-the-shelf” CART cells
  - Increasing efficacy/therapeutic index

- Combinations (e.g., CART plus “checkpoint” inhibitors)
Therapeutic Immuno-oncology Approaches
Selected Examples from Industry and the Novartis Immuno-oncology Portfolio

- Talimogene
- STING
- PD1/PDL1
- LAG-3
- CART therapy
- IDO
- CSF-1
Targeting the immunosuppressive tumor microenvironment

*Indoleamine and tryptophan dioxygenases*

- IDO/TDO promotes accumulation of Kynurenine, immunosuppressive byproduct of tryptophan catabolism and promotes tumor evasion

- IDO activity promotes an immunosuppressive environment within tumors by upregulating trafficking of myeloid-derived suppressor cells (MDSC) and Tregs

- Overexpression of IDO1 is associated with adverse clinical outcomes
Targeting the immunosuppressive tumor microenvironment

Colony stimulating factor -1

- Tumor-secreted CSF1 recruits tumor-associated macrophages, which can regulate tumor growth, angiogenesis, invasion, and/or metastasis
- MCS110 is a humanized monoclonal antibody that binds to CSF1 and blocks its ability to recruit TAMs
- A planned Phase II study will assess whether the inhibition of macrophages by MCS110 enhances chemotherapeutic efficacy in patients with TAM-high advanced triple-negative breast cancer

**Trial ID**

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<th>Phase</th>
<th>N</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02435680</td>
<td>MCS110 plus carboplatin/gemcitabine in advanced triple-negative breast cancer with high TAMs</td>
<td>2</td>
<td>≈78</td>
<td>• PFS</td>
</tr>
<tr>
<td>NCT01643850</td>
<td>Pigmented villonodular synovitis or giant cell tumor of the tendon sheath</td>
<td>2</td>
<td>≈18</td>
<td>• Change in tumor size • Safety</td>
</tr>
</tbody>
</table>

Therapeutic Immuno-oncology Approaches
Selected Examples from Industry and the Novartis Immuno-oncology Portfolio

- Talimogene
- STING
Talimogene laherparepvec (T-VEC)
Approved by the FDA in October 2015

- Talimogene laherparepvec is an oncolytic, engineered herpesvirus with modifications that increase its therapeutic value
  - Removal of neurovirulence factor prevents neurotoxicity
  - Addition of GM-CSF promotes dendritic function
  - Deletion of ICP47 promotes oncolysis and viral replication

Andtbacka et al., JCO 2015
Local delivery may lead to systemic therapy

*The abscopal effect*

- Inflammation (innate immunity)
- Abscopal response (adaptive immunity)

Johnson et al, 2015, Drug Evaluation
STING
Stimulator of interferon genes

- STING is a central sensor of cytosolic double-stranded nucleic acids from infectious pathogens, and is essential for efficient induction of a type I interferon immune response\(^1,2\)
- STING senses and binds to bacterial signaling molecules known as cyclic dinucleotides (CDNs),\(^3\) which leads to the expression of T-cell recruitment factors, including pro-inflammatory cytokines and interferon\(^1\)
- CDNs may be useful as vaccine adjuvants, given the strong immune response triggered by foreign double-stranded DNA\(^1,4\)
- In mouse tumor models, intratumoral injections of synthetic CDNs resulted in a substantial regression of injected and distant tumors, and provided immunologic memory\(^5\)

DC, dendritic cell; TME, tumor microenvironment.

ADU-S100

A STING agonist for enhancing immune response to tumors

- ADU-S100, a STING agonist, is a CDN delivered to the tumor by direct injection with the potential to be a first-in-class therapy\(^1\)

STING agonist (CDN) injection into tumors eliminates both injected and non-injected tumors

ADU-S100 (partnership with Aduro) effectively “immunizes” the mouse to tumors

Surgery, radiation and chemotherapy remain the foundation of cancer treatment.

Targeted therapies often demonstrate profound, but not durable, clinical responses in genetically selected patients.

Immune-modulators such as “checkpoint” inhibitors have demonstrated durable responses, but not in all patients.

Cell therapy has shown durable responses in select patient populations, but the current technology may not be generalizable to all tumor types.

Innovative immuno-therapies and combinations of those therapies outlined above are aimed at establishing and maintaining a memory response to tumors in patients; a response that may lead to durable remission.
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