Gene Therapies and Immunotherapy Updates in Solid Tumor Malignancies

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Objectives

1. Understand the role that gene therapies currently play in the treatment of solid tumors
2. Recognize the shift in the treatment landscape of solid tumors from chemotherapy to the incorporation of immunotherapy

Definitions

Gene therapy: “seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use”

Immunotherapy: stimulates the immune system to fight cancer by enhancing ability to recognize and eliminate harmful cells, while minimizing damage to healthy tissues

What is Gene Therapy? Food & Drug Administration. Updated 7/25/2018. Accessed 5/1/23. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy

Gene Therapy

Talimogene laherparepvec (T-VEC)

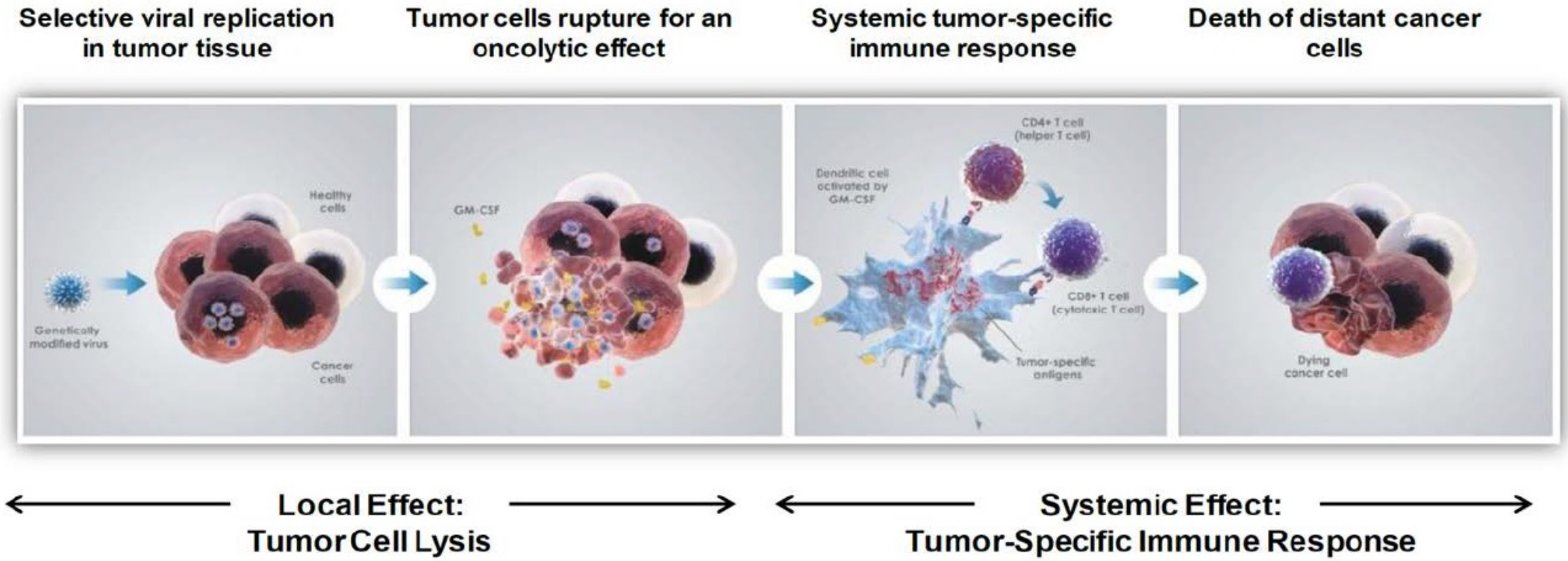
T-VEC

Genetically modified oncolytic viral therapy

- Derived from novel primary HSV-1 isolate
- Deletion of virulence genes which code for ICP34.5 (reduces virulence) and ICP47 (permits proper antigen processing for both virus and tumor antigens)
- Addition of human GM-CSF (further increases immune recognition)

T-VEC

Mechanism of Action



Cancers (Basel). 2021;13(6):1383.

Place in Therapy

FDA Indication

Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery

NCCN Recommendations

- Stage III in-transit or local satellite/in-transit recurrence
  - Limited resectable (Category 2A)
  - Unresectable (Category 1)
- Metastatic disease (Category 2A)
  - For accessible lesions

OPTiM trial randomized patients 2:1 to receive T-VEC or GM-CSF
Durable response rate (DRR): 19% vs 1.4% **Overall response rate (ORR):** 31.5% vs 6.4%
Stage IIIB/IIIC DRR: 33% vs 0%
Treatment-naïve patients saw greater benefit

J Immunother Cancer. 2019;7(1):145.
NCCN. Cutaneous Melanoma. V2.2023. Accessed 5/1/23.

Dosing & Administration

T-VEC
10 ^ 6 PFU/mL

Nadofaragene firadenovec

Ferring Press Release 2022. Accessed 5/5/23
NCCN. Bladder Cancer V 2.2023. Accessed 5/5/23

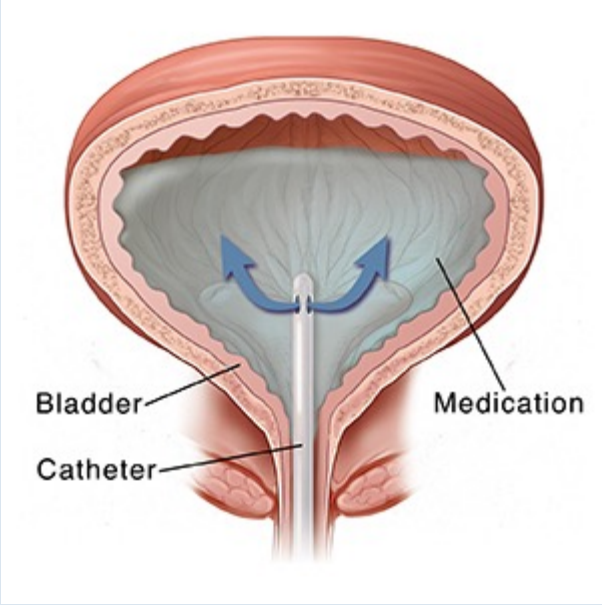
How it works

Transports a copy of **interferon alfa-2b gene** and **Syn3**, a polyamide surfactant that augments transfer into cancer cells

Intravesicular: bladder instillation every 3 months, up to 12 months

Study CS-003:

- CRR: 53.4% at 3 months
- Median DoR: 9.7 months
- Anti-adenovirus antibody level may predict durable responses



Lancet Oncol. 2021;22(1):107-117
Eur Urol. 2022;81(3):223-228

Safety

Most common drug-related ADRs:

Immunotherapy

Updates in Solid Tumors

Site-Agnostic Indications

Pembrolizumab

GI: Durvalumab

Biliary Cancer

FDA approved September 2022

First-line in combination with gemcitabine + cisplatin

TOPAZ-1 trial: improved overall survival (median OS 12.8 vs 11.5 months)

Hepatocellular Carcinoma

FDA approved October 2022

First-line in combination with tremelimumab (anti CTLA-4)

HIMALAYA trial: improved overall survival compared to sorafenib (median OS 16.4 vs 13.8 months)

FDA Drug Approvals & Databases. Current as of 9/2/22 and 10/24/22. Accessed 5/5/23

GU: Pembrolizumab

New Duo in Melanoma

Relatlimab-rmbw & nivolumab

Fixed-dose dual immunotherapy combination approved in March 2022 for the treatment of unresectable or metastatic melanoma in adult and pediatric patients ≥12 years of age

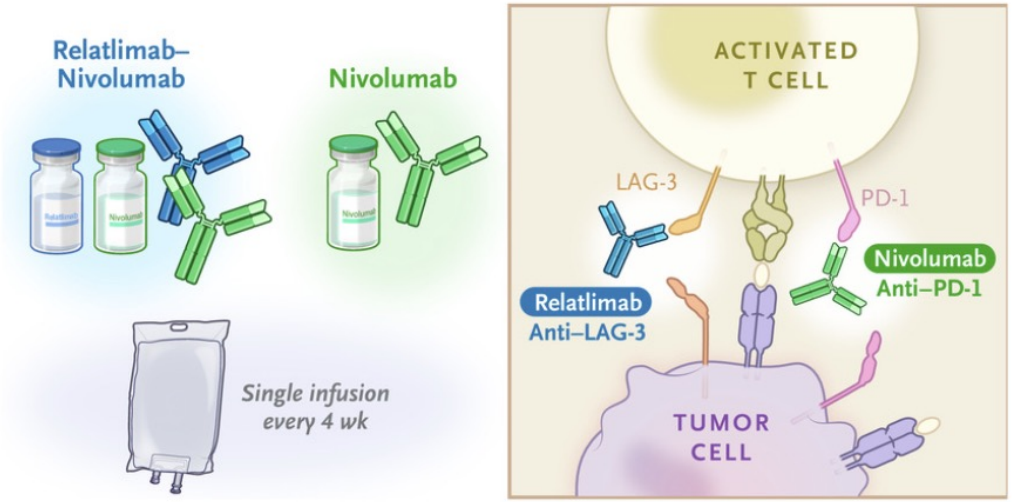
- Relatlimab: anti-LAG-3
- Nivolumab: anti-PD-1

Oncology (Cancer) / Hematologic Malignancies Approval Notifications. Updated 4/20/23. Accessed 5/2/23.

Relatlimab & Nivolumab

Mechanism of Action

- Relatlimab is a **Lymphocyte Activating Gene 3 (LAG-3) blocking antibody**. LAG-3 is expressed on the surface of T cells and when blocked, promotes T cell proliferation and cytokine secretion.
- Nivolumab is a **Programmed Death 1 (PD-1) blocking antibody** which blocks the interaction of PD-1 on T cells with PD-L1 on tumor cells, allowing for T cell activation & proliferation.
- **Combining anti-PD-1 and anti-LAG-3 results in increased T-cell activation compared to the activity of either antibody alone!**



N Engl J Med. 2022;386(1):24-34.

Place in Therapy

NCCN

Metastatic or unresectable disease

- First line (Category 1)
- Subsequent (Category 2A)

Available Alternatives

- Nivolumab + ipilimumab
- Nivolumab
- Pembrolizumab
- BRAF/MEK inhibitors
- Pembrolizumab + ipilumumab (low dose)

When to use?

- May not tolerate therapy with anti-CTLA4
- Desired dual immune checkpoint blockade
- Disease progression on prior lines of therapy

RELATIVITY-047 randomized patients with previously untreated unresectable stage III or IV melanoma to relatlimab-nivolumab or nivolumab alone every 4 weeks
Progression-free survival (PFS): 10.1 vs 4.6 months **PFS at 12 months**: 47.7% vs 36%
Grade 3/4 TRAEs: 18.9% vs 9.7% **Myocarditis:** 1.7% vs 0.6%

NCCN. Cutaneous Melanoma. V2.2023. Accessed 5/1/23.
N Engl J Med. 2022;386(1):24-34.

Non-small Cell Lung Cancer

Latest advancements in neoadjuvant & adjuvant setting

Neoadjuvant

Nivolumab (anti-PD-1) plus histology-based chemotherapy

- CheckMate816

Adjuvant

Atezolizumab (anti-PD-L1)

- IMpower010

Pembrolizumab (anti-PD-L1)

- PEARLS/KEYNOTE-091

NCCN. Non-small cell lung cancer. V3.2023. Accessed 5/3/23.

Neoadjuvant Nivolumab + Chemo

Recommended to evaluate patients with stage IB (> 4 cm) to IIIA NSCLC for perioperative therapy

- Administered every 3 weeks for 3 cycles in combination with chemotherapy below

Nonsquamous

- Cisplatin/Carboplatin + pemetrexed

Squamous

- Cisplatin/Carboplatin + gemcitabine

Any

- Cisplatin/Carboplatin + paclitaxel

NCCN. Non-small cell lung cancer. V3.2023. Accessed 5/3/23.

Neoadjuvant Nivolumab + Chemo

CheckMate816

Patients with known *EGFR* mutations or *ALK* translocations excluded

Randomized 1:1 to nivolumab + chemotherapy or chemotherapy alone

- **Event-free survival (EFS):** 31.6 vs 20.8 months
  - Magnitude of benefit greatest in stage IIIA disease and PD-L1 > 1% but still consistent across groups
- **Pathological complete response (PCR):** 24% vs 2%

Surgical Outcomes

- Definitive surgery: 83% vs 75%
- Minimally invasive surgery: 30% vs 22%
- Lobectomy: 77% vs 61%
- Pneumonectomy: 17% vs 25%

No increase in median duration of surgery or length of hospitalization

N Engl J Med. 2022;386(21):1973-1985.

Adjuvant Immunotherapy

Atezolizumab

Following previous adjuvant systemic therapy, may be administered for up to 1 year, for patients with **PD-L1 ≥ 1%**

- Completely resected stage IIB-IIIA, stage IIIB, or high-risk stage IIA NSCLC

IMpower010 showed disease-free survival benefit

Pembrolizumab

Following previous adjuvant systemic therapy, may be administered for up to 1 year, **regardless of PD-L1 expression**

- NCCN recommends for completely resected stage IIB-IIIA, stage IIIB, or high-risk stage IIA
- FDA approval includes stage IB(> 4 cm)

Event-free survival improved in overall population

Lancet. 2021;398(10308):1344-1357.
Lancet Oncol. 2022;23(10):1274-1286.

Future Directions

What is the role of combined neoadjuvant and adjuvant immunotherapy?

- NADIM (NCT03081689): Combines neoadjuvant nivolumab + chemotherapy followed by adjuvant nivolumab for 1 year
- KEYNOTE-671 (NCT03425643): Combines neoadjuvant pembrolizumab + chemotherapy up to 4 cycles, followed by adjuvant pembrolizumab for up to 13 cycles
- LCMC3 (NCT02927301): Patients received 2 cycles of neoadjuvant atezolizumab monotherapy and following resection, could continue adjuvant atezolizumab for up to 12 months

Summary

Gene therapies in solid tumors are very limited at this time, but they present a novel way of achieving improved outcomes.

Immunotherapy has become the gold standard in all aspects of solid tumor treatment and has also greatly improved outcomes in cancer patients.

Thank you

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