Sarcoma Patient
Advocacy Global Network
e.V./Assoc.
Administration-Office
Untergasse 36
D-61200 Wölfersheim Germany
Fon: 0049-089-62836807 Fax: 0049-089-62836808
info@sarcoma-patients.org
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Immune-Based and Tumor Antigen-Directed Therapies in Sarcomas: Mechanisms of Action, Clinical Use, and Main Adverse Effects

1. Introduction

The immune system is a highly sophisticated defense system that helps the body recognize and destroy abnormal cells, including cancer cells. However, tumors are often able to hide from the immune system or block its response. They can do this in several ways, such as sending signals that slow down immune responses, releasing substances that weaken immune activity, or creating a protective environment that prevents immune cells from reaching an effectively attacking the tumor.

Modern **immune-based** therapeutic strategies aim to restore or enhance anti-tumor immunity, either by modulating endogenous immune responses or by supplying ex vivo–engineered immune effector cells**.**
In parallel, **tumor antigen-directed therapies** are emerging to deliver cytotoxic drugs or radiation directly to cancer cells via antibodies recognizing tumor-associated antigens. These therapies are also labelled as "**targeted therapies**", a broad definition that encompasses treatments designed to selectively interfere with tumor-specific molecular features, including a class of "**small molecules**" that are targeted intracellular pathway modulators. These small molecules alter tumor biology by inhibiting intracellular oncogenic or epigenetic signaling rather than directly killing cells, and work best when there is a dominant mutation (*e.g. GIST, epithelioid sarcoma).*
Although tumor antigen-directed therapies fall under "targeted therapies", they totally differ from small molecules in structure and mechanism, as highlighted in the table below. Basically, although both **small molecules** and **antigen-directed therapies** act on **specific molecular targets**—unlike non-specific chemotherapy—**small molecules** are tiny compounds that **enter cells**, target **intracellular proteins (enzymes or kinases)**, and **directly inhibit cancer signaling** without involving the immune system.

Table: Key Differences Between Small Molecules and Antigen-Directed Therapies

Feature	Small-Molecule Targeted Therapies	Antigen-Directed Targeted Therapies
Drug type	Small chemical compounds	Protein-based drugs (antibodies)
Size	Very small	Large molecules
Cell entry	Can enter cells	Mostly extracellular (cannot enter cells easily)
Target location	Intracellular proteins (enzymes, kinases)	Cell-surface antigens or immune checkpoints
Mechanism of action	Directly inhibit signaling pathways	Block signals, activate immune killing, or modulate immune checkpoints
Immune system involvement	None	Often involved
Selectivity	Based on molecular structure of the target	Based on antigen recognition
Administration	Often oral	Usually intravenous
Examples	TRK inhibitors,	Monoclonal antibodies, ADCs, PD-1/PD-L1 inhibitors

In **sarcomas,** the application of these therapies is particularly challenging due to their biological heterogeneity, variable immune landscapes, and diverse molecular drivers. Nevertheless, these approaches are increasingly explored, especially in advanced or treatment-resistant disease. In selected sarcoma subtypes such as **metastatic alveolar soft part sarcoma (ASPS)**, immune-based therapy may be considered **first-line**, while in most others, immunotherapy is reserved for later lines or within clinical trials.

2. Types of Therapies and Sarcomas

2.1 Immune-Based Therapies include:

2.1.1 Immunotherapy (Checkpoint Inhibitors), which harnesses and enhances the patient's own immune system to recognize and destroy cancer cells by blocking inhibitory pathways (PD-1/PD-L1, CTLA-4), "releasing the brakes" on T cells, and enabling effective anti-tumor immune response.

Sarcoma examples:

- *ASPS (first-line in metastatic disease)*
- *Undifferentiated pleomorphic sarcoma (UPS; selected metastatic cases)*
- *Less effective in synovial sarcoma, myxoid liposarcoma*

2.1.2 Adoptive Cellular Therapies (ACT) which involve engineering autologous (the patient's own) or allogeneic (from a donor) immune cells (T lymphocytes) to directly attack tumors. Typically patient's T cells are collected, genetically modified and expanded ex vivo, and reinfused into the patient. ACT include both chimeric (*chimeric: a mixed, custom-made receptor that is artificially built to give these cells a new ability against cancer cells*) antigen receptor (CAR)-T cells and T cell receptor (TCR)-engineered T cells.

- **CAR-T cells** that recognize and bind **tumor surface antigens** independently of HLA_presentation and exert cytotoxic activity. CAR-T therapy has revolutionized hematologic malignancies; solid tumor application, including sarcomas, are under investigation with limited efficacy to date.
  Investigational in sarcomas:
  -Targets: HER2 (osteosarcoma), GD2 (Ewing sarcoma), B7-H3 (various sarcomas).
- **TCR-engineered T cells (TCR-T):** T cells modified to express receptors that recognize **intracellular antigens** presented by HLA molecules.
  Sarcoma examples:
  NY-ESO-1 or MAGE-A4 targeting in synovial sarcoma and myxoid/round cell liposarcoma.

2.2 Tumor Antigen-Directed Therapies

Antibody-drug conjugates and radioligand therapies act as **targeted delivery systems** for **cytotoxic drugs or radiation**. They target cell surface antigens thereby preferably requiring high stable antigen expression**.** They act independently of the patient's immune system and rely on selective delivery of cytotoxic drugs or radiation by using **antibodies** against tumor-associated antigens.

2.2.1 Antibody-Drug Conjugates (ADCs): Deliver cytotoxic payloads to tumor cells expressing specific antigens.
Sarcoma examples:
Trastuzumab deruxtecan in HER2-positive osteosarcoma or angiosarcoma.

2.2.2 Radioligand Therapies: Radioactive isotopes linked to tumor-targeting molecules deliver localized radiation.
Sarcoma examples:
Experimental in sarcomas expressing SSTR2.

3. Factors Influencing Therapy Effectiveness in Sarcomas

In sarcomas, effectiveness of all these therapies depends on multiple, often interrelated biological and clinical factors. Among those, there are:

- **Molecular profile of sarcoma subtype**
- **Tumor immune profile:**
  - The immune context – commonly described as immune-hot or immune-cold- strongly influences responsiveness to immune-based therapies.
  - **Immune-hot tumors:** High T-cell infiltration, PD-L1+, high mutational burden; respond to checkpoint inhibitors (ASPS, some UPS).
  - **Immune-cold tumors:** Poorly infiltrated, immunosuppressive; may require ACT or antigen-directed therapies (synovial sarcoma, myxoid liposarcoma, GIST).
- **Tumor antigen expression:** the presence, density and homogeneity of tumor-associated antigens are critical for responsiveness to CAR-T, TCR-T, ADCs, radioligands.
- **Tumor antigenicity and tumor mutational burden (TMB)**
- Higher tumor mutational burden and increased neoantigen load play a crucial role in responses to immunotherapy (checkpoints inhibitors)
- **Tumor microenvironment:** Features of the tumor microenvironment- such as stromal density, vascular architecture, immunosuppressive cells- can impede immune infiltration and thus limit efficacy of treatments.
- **Prior treatments & disease characteristics:** Previous treatments- such as chemotherapy radiotherapy or targeted agents- as well as tumor burden, growth kinetics, and metastatic pattern can affect responsiveness.
- **Patient-related factors:** Performance status, patient immune competence, co-morbidities as well as ability to tolerate and complete complex therapies can play an important role for treatment success.

4. Clinical Use, Mechanisms of Action, and Main Adverse Effects in Sarcomas

In sarcomas, *first-line* treatment remains surgery, chemotherapy, or targeted therapy (small molecules), except for metastatic ASPS, where immune-based therapy can be considered upfront. Immunotherapeutic approaches continue to be evaluated for various subtypes of sarcoma in clinical trials.

Immune-based and tumor antigen-directed therapies (ADC and radioligand therapies) have distinct adverse effects: immune-based therapies may cause mostly immune-mediated organ inflammation, while antigen-directed therapies may cause cytotoxic or radiation-related toxicity.

Therapy Type	Mechanism of Action	Immune Dependence	Sarcoma Examples	Main Adverse Effects
Immunotherapy (Immune Checkpoint Inhibitors)	Block PD-1/PD-L1 or CTLA-4 to **restore T-cell activity**	Yes	-ASPS (first-line in metastatic), -UPS (selected metastatic); -Synovial sarcoma, myxoid liposarcoma (less responsive)	Immune-mediated inflammation: colitis, pneumonitis, hepatitis, endocrinopathies
CAR-T cells	T cells engineered with chimeric receptors to bind **surface antigens** (**HLA-independent**)	Yes	HER2-positive osteosarcoma, GD2-positive Ewing sarcoma, synovial sarcoma (investigational)	Cytokine release syndrome, neurotoxicity, prolonged cytopenias, infections
TCR-engineered T cells (**TCR- T**)	T cells engineered to recognize **intracellular antigens** (**HLA-dependent)**	Yes	NY-ESO-1: synovial sarcoma, MRCLS; MAGE-A4: synovial sarcoma	Cytokine release syndrome, neurotoxicity, prolonged cytopenias, infections
Antibody-Drug Conjugates (**ADCs**)	**Antibody delivers cytotoxic drug** to tumor cells expressing specific antigens	No	Trastuzumab deruxtecan: HER2-positive osteosarcoma, angiosarcoma	Payload-dependent toxicity (e.g. myelosuppression, neuropathy, liver toxicity, infusion reactions)
Radioligand therapies	Radioactive isotope linked to tumor-targeting molecules **delivers localized radiation**	No	Radiolabeled SSTR2 ligands (experimental)	Myelosuppression, fatigue, organ-specific radiation toxicity

5. Treatment Decision Strategy

There is no one-size-fits-all therapy in sarcomas; treatment decisions must integrate tumor biology, molecular features, immune context, and patient-specific factors.

Therefore, treatment selection is **highly personalized**, mainly based on:

1. Sarcoma subtype & molecular features
2. Tumor immune profile (*hot vs cold*)
3. Antigen expression
4. Prior treatments & patient-related factors

Combination strategies are under investigation:
Clinical trial enrollment is strongly recommended for patients with advanced or treatment-resistant sarcomas, especially for immune-cold tumors or investigational targets.