Clinical Trials and Immunotherapy for Sarcomas
Sarcoma Exchange
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Clinical Trials are experiments to assess the value of a treatment

Essentially all anti-cancer drugs currently available have gone through the clinical trials process

The process is designed to select drugs which are both safe and effective and protect the public from ineffective or harmful agents. These are therapeutic trials

Clinical trials can also be used to test the impact of lifestyle changes on certain disease states or look for markers of disease in blood or tissue specimens. These are non-therapeutic trials
Why bother with Clinical Trials?

The alternative is the anecdote-”I heard drug X works great against the Coronavirus”
Clinical Trials for new drug approval are an arduous process

Only 3.3% of drugs successfully negotiate the clinical trials process and become approved agents.

When the drug has a specific known target, the success rate improves to approximately 10%.

The cost of bringing a new drug through the approval process is estimated at approximately $648 million (range $157.3 million to $1950.8 million).

Median time to develop a new cancer drug is 7.3 years.
What are the phases of Clinical Trials?

Phase 1 trials are the initial studies of a drug in people. These agents are selected for study based upon pre-clinical evaluation in the laboratory.

Often these are first-in-human studies.

Typically start with a low dose based upon information from animal studies.

Dose Escalation to look for any unacceptable side effects and to find a recommended dose and schedule for phase 2 study-RP2D.

Phase 1 studies also look to see how the agent is metabolized and distributed in the body.

Not designed to test for efficacy. However approximately 6% of patients on phase 1 studies derive a clinical benefit.
Phase 1 trials

These are generally small trials with a limited number of participants.

In the past these trials were open to a wide variety of patients whose disease had progressed on all known active agents or whose disease had no established effective treatment.

Thus a phase 1 trial might include patients with lymphoma, carcinoma, sarcoma and melanoma.

With the advent of targeted therapies, some phase 1 trials limit participation to subjects with known or suspected targets, potentially limiting access for sarcoma patients to some clinical trials.

Some trials are now disease agnostic and can include all disease types with a specific marker. Example-recent studies of NTRK fusions entered patients across multiple tumor types.
Phase 2 Trials

These are trials which build upon the knowledge gained from the Phase 1 trial.

They test the agent against a specific disease or target.

These trials seek to determine the efficacy of the drug and generally include a larger number of patients than Phase 1 studies.

Sometimes Phase 1b/2 studies are designed to seamlessly progress from one to the other.

These studies are used to make the Go/No Go determination to proceed to a phase 3 study.
Phase 3 Trials

These are larger trials designed to test the new agent against the existing standard of care or against a placebo if no standard treatment exists.

To determine if the new regimen is “better”

“Better” will be designated by the trial endpoint-Progression Free Survival, Overall Survival, Less Toxicity, Quality of Life

Large, expensive trials which can be multi-center or multi-national

Successful completion of a Phase 3 trial is used to obtain regulatory approval for the agent to be marketed for use.
Complete Response—Complete disappearance of all target lesions. Any pathologic lymph nodes must have reduction in short axis to < 10mm.

Partial Response—At least a 30% reduction in the sum of diameters of target lesions, taking as a reference baseline sum parameters.

Progressive Disease—At least a 20% increase in the sum of diameters of target lesions. New lesions.

Stable Disease—Neither sufficient shrinkage to qualify for PR or sufficient growth to qualify for PD.

Clinical Benefit Rate—Combines Complete Response, Partial Response and Stable Disease.
Doxorubicin and Olaratumab for Advanced Sarcoma

Phase 1b-2 Study

Tap Lancet Oncology 2016

Cedars Sinai
Conclusion: Single Agent Doxorubicin still The “Gold Standard” for advanced soft tissue sarcoma. Olaratumab has been withdrawn from use.
Phase 4 trials are conducted on already approved agents and may look at issues such as long-term effects.
What are the components of a good clinical trial?

- Sound science
- Free of bias
  - Randomization
  - Blinded/Double Blinded
  - Placebo Controlled (May allow crossover)
  - Independent Central Review
Clinical Trial Participation

Approximately 2-7% of adult cancer patients enter clinical trials.

Approximately 60% of child cancer patients enter clinical trials usually sponsored through the Children’s Oncology Group.

Klabunde et al. South Med J 1999
Children’s Oncology Group website
Advantages to Clinical Trial Participation

Access to new treatments before they are commercially available

Access to expert physicians with specific knowledge of their disease

Altruism—goal of helping others in the future to move medicine forward (particularly true for Phase 1 studies)
Disadvantages of Clinical Trial Participation

New agent can have side effects or unacceptable toxicity

New agent may be inferior to existing agent(s) or placebo

May wind up on placebo arm with no crossover
Barriers to Clinical Trial Participation

Structural-No trial available

Clinical-Patient Ineligible

Physician-Offered/Not offered to patient

Patient-
  Desire to determine own treatment
  Loss of Control-Don’t want to be a “guinea pig”
  Fear of side effects
  Concerns about Costs
  Logistical barriers-transportation
How to Find a Clinical Trial

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

Explore 388,717 research studies in all 50 states and in 219 countries.

Find a study

Status

- Recruiting and not yet recruiting studies
- All studies

Condition or disease

Other terms

Country

Search

Advanced Search
Immunotherapy

Goal of harnessing the body’s immune system against a malignant tumor

Not a new concept-Dr. Coley was head of the Bone Tumor service at Memorial Hospital in NY. Joined the staff in 1890s and learned of a patient with a malignant head and neck tumor which regressed after the patient developed erysipelas. He examined the patient and found no evidence of cancer.

He then began injecting patients heat-killed Streptococcus and Serratia marcescens which became known as Coley’s toxin.

Dr. William Coley
Three Potential Ways to Target the Immune System

Immune Checkpoint Agents-designed to unleash the immune system

- PD1, PDL1 agents
- CTLA-4 antibodies

Vaccines

- Target a marker on the tumor cell, NY ESO-1

Adoptive Cell Therapy

- CAR-T cells Chimeric Antigen Receptor
- T cells transduced with T cell receptor directed against NY ESO-1, HER2
- Spear T cells-specific peptide enhanced antibody receptor
Immunotherapy
# Immunotherapy Trials in Soft Tissue Sarcomas

## Table 1: Selected completed immunotherapy studies in soft-tissue sarcoma (STS)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Agent</th>
<th>Phase</th>
<th>Pts (n)</th>
<th>Indication</th>
<th>Response rate</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Checkpoint inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maki et al., 2013</td>
<td>Ipilimumab</td>
<td>I</td>
<td>6</td>
<td>Advanced SynS</td>
<td>0 of 6</td>
<td>mOS: 8.75 months</td>
</tr>
<tr>
<td>Tawbi et al., 2017</td>
<td>Pembrolizumab</td>
<td>II</td>
<td></td>
<td>Selected STSs and bone sarcomas</td>
<td>10% in STS; 40% in UPS; 20% in LPS; 10% in SynS</td>
<td>mPFS: 18 weeks; OS: 49 weeks</td>
</tr>
<tr>
<td>D’Angelo et al., 2018</td>
<td>Nivolumab with or without ipilimumab</td>
<td>II</td>
<td>96</td>
<td>Metastatic STS</td>
<td>Nivolumab: 5%; Ipilimumab–nivolumab: 16%</td>
<td>mPFS: 4.1 months; OS: 14.3 months</td>
</tr>
<tr>
<td>Toulmonde et al., 2018</td>
<td>Pembrolizumab, cyclophosphamide</td>
<td>II</td>
<td>57</td>
<td>Advanced STS</td>
<td>Solitary fibrous tumour in 1 patient</td>
<td>NA</td>
</tr>
<tr>
<td>Wilky et al., 2019</td>
<td>Axitinib, pembrolizumab</td>
<td>II</td>
<td></td>
<td>ASPS and other STSs</td>
<td>25%, all STS patients; 50.4%, ASPS patients</td>
<td>3-Month PFS: 66%; in ASPS patients: 73%</td>
</tr>
<tr>
<td><strong>Adoptive cell therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robbins et al., 2011</td>
<td>Adoptively transferred autologous T cells transduced with a T cell receptor directed against NY-ESO-1</td>
<td>I</td>
<td>6</td>
<td>Metastatic SynS expressing NY-ESO-1</td>
<td>4 of 6</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Vaccines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malvi et al., 2002</td>
<td>Tumour cells treated with granulocyte macrophage colony-stimulating factor</td>
<td>I</td>
<td>16</td>
<td>Melanoma and sarcoma</td>
<td>1 of 16</td>
<td>NA</td>
</tr>
<tr>
<td>Dillman et al., 2004</td>
<td>Autologous tumour cell-line-derived vaccines</td>
<td>I/II</td>
<td>23</td>
<td>Recurrent or metastatic sarcoma</td>
<td>No objective response</td>
<td>10 Patients lived more than 1 year</td>
</tr>
<tr>
<td>Kawaguchi et al., 2005</td>
<td>Vaccination with SYT-SSX junction peptide</td>
<td>I</td>
<td>6</td>
<td>Metastatic SynS</td>
<td>0 of 6</td>
<td>NA</td>
</tr>
<tr>
<td>Finkelstein et al., 2012</td>
<td>Radiotherapy with intralesional injection of dendritic cells</td>
<td>I/II</td>
<td>17</td>
<td>Neoadjuvant treatment in high-risk STS</td>
<td>9 of 17</td>
<td>1-Year PFS: 70.6%</td>
</tr>
<tr>
<td>Kawaguchi et al., 2012</td>
<td>SYT–SSX breakpoint peptide vaccines</td>
<td>I/II</td>
<td>21</td>
<td>Metastatic SynS</td>
<td>1 of 21 (stable disease: 6 of 21)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Pts = patients; SynS = synovial sarcoma; mOS = median overall survival; UPS = undifferentiated pleomorphic sarcoma; LPS = liposarcoma; mPFS = median progression-free survival; OS = overall survival; NA = not applicable; ASPS = alveolar soft-part sarcoma; PFS = progression-free survival.
Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial

<table>
<thead>
<tr>
<th>Sarcoma Subtype</th>
<th>Complete response</th>
<th>Partial response</th>
<th>Stable disease</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue sarcomas (n=40)</td>
<td>1 (3%)</td>
<td>6 (15%)</td>
<td>15 (38%)</td>
<td>18 (45%)</td>
</tr>
<tr>
<td>Leiomyosarcoma (n=10)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>6 (60%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Undifferentiated pleomorphic sarcoma (n=10)</td>
<td>1 (10%)</td>
<td>3 (30%)</td>
<td>3 (30%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Liposarcoma (n=10)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
<td>4 (40%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Synovial sarcoma (n=10)</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
<td>2 (20%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Bone sarcomas (n=40)</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
<td>9 (23%)</td>
<td>29 (73%)</td>
</tr>
<tr>
<td>Chondrosarcoma (n=5)</td>
<td>0 (0%)</td>
<td>1 (20%)</td>
<td>1 (20%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Ewing's sarcoma (n=13)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (15%)</td>
<td>11 (85%)</td>
</tr>
<tr>
<td>Osteosarcoma (n=22)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>6 (27%)</td>
<td>15 (58%)</td>
</tr>
</tbody>
</table>

Data are n (%).

Table 2: Best response in 80 evaluable patients by sarcoma histological subtype
Figure 4: Best percentage change from baseline in size of target lesions in patients with bone sarcoma. Tumour sizes were calculated as the sum of target lesion diameters. Data for two patients with Ewing's sarcoma and three patients with osteosarcoma are not shown because they did not have a second scan.
Figure 2: Best percentage change from baseline in size of target lesions in patients with soft-tissue sarcoma.

Tumour sizes were calculated as the sum of target lesion diameters. Data for two patients with synovial sarcoma and one patient with liposarcoma are not shown because they did not have a second scan.
Immune Checkpoint Inhibitors Appear To Be Most Active in Cutaneous Angiosarcoma, Chordoma and Alveolar Soft Part Sarcoma
Pembrolizumab in cutaneous angiosarcoma
Toxicity of Immune Checkpoint Inhibitors

- Usually well tolerated compared to chemotherapy
- Pneumonitis - cough or shortness of breath
- Colitis - diarrhea, abdominal pain
- Nephritis
- Immune endocrine disorders - hypothyroidism, hypopituitarism
- Cerebritis - confusion, memory problems
- Patients with existing connective tissue diseases can have worsening of symptoms
Pseudoprogression is the temporary enlargement of a tumor following administration of an Immune checkpoint inhibitor. May be related to an influx of immune cells into the tumor region. Will subside with time.

Hyperprogression is the paradoxical accelerated growth of a tumor after exposure to an immune checkpoint agent. May occur in up to 30% of cases. Associated with older age, tumors with MDM2 overexpression, prior exposure to radiation. Mechanism is not well understood.
Need a better understanding of the science

“Hot” tumors, “Cold” Tumors-Can a cold tumor be made into a hot tumor?

Carcinomas which respond well to Immune Agents often have high mutational burdens

Many sarcoma have low mutational burdens and have amplifications and translocations as opposed to mutations

Combinations of Immune Agents with chemotherapy, tyrosine kinase inhibitors, radiation

Possible use of Multiple Immune Agents-Vaccine + Immune Checkpoint Agent
Clinical Trials.gov open trials for adult soft tissue sarcoma