Clinical Trials and Immunotherapy for Sarcomas Sarcoma Exchange September 11, 2021

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What are Clinical Trials?

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

Prasad et al JAMA Intern Med 2017

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 Phase1b/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

Assessment of Response on Clinical Trials
RECIST 1.1
Response Evaluation Criteria in Solid Tumors

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

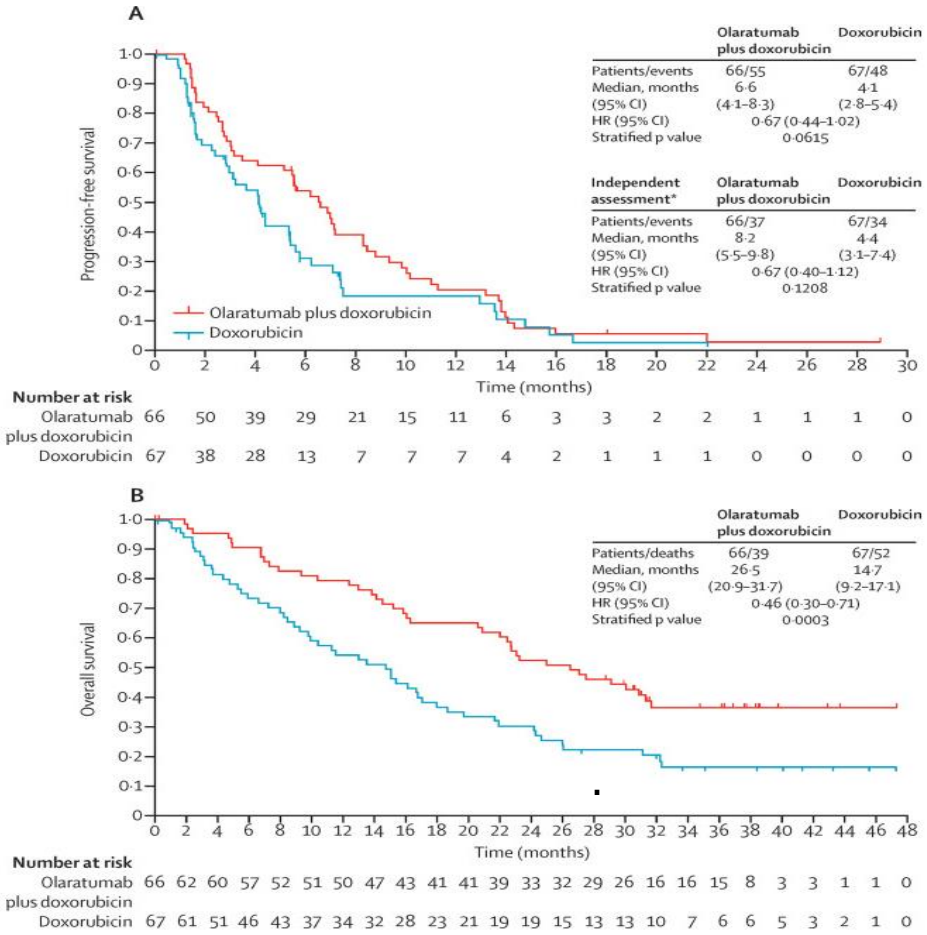
Stable Disease-Neither sufficient shrinkage to qualify for PR or sufficient growth to qualify for PD

Clinical Benefit Rate-Combines Complete Response, Partial Response and Stable Disease

Eisenhauer EA et al Eur J Cancer 2009

Doxorubicin and Olaratumab for Advanced Sarcoma

Phase 1b-2 Study

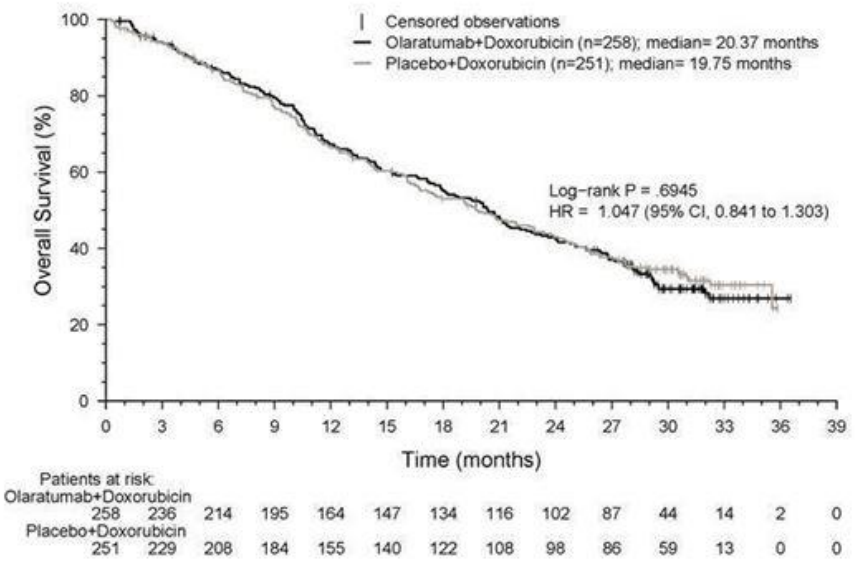


Tap Lancet Oncology 2016

Cedars Sinai

Doxorubicin and Olaratumab for Advanced Sarcoma

Phase 3 Study



Conclusion: Single Agent Doxorubicin still The “Gold Standard” for advanced soft tissue sarcoma. Olaratumab has been withdrawn from use.

Tap Lancet Oncology 2016

Phase 4 trials

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

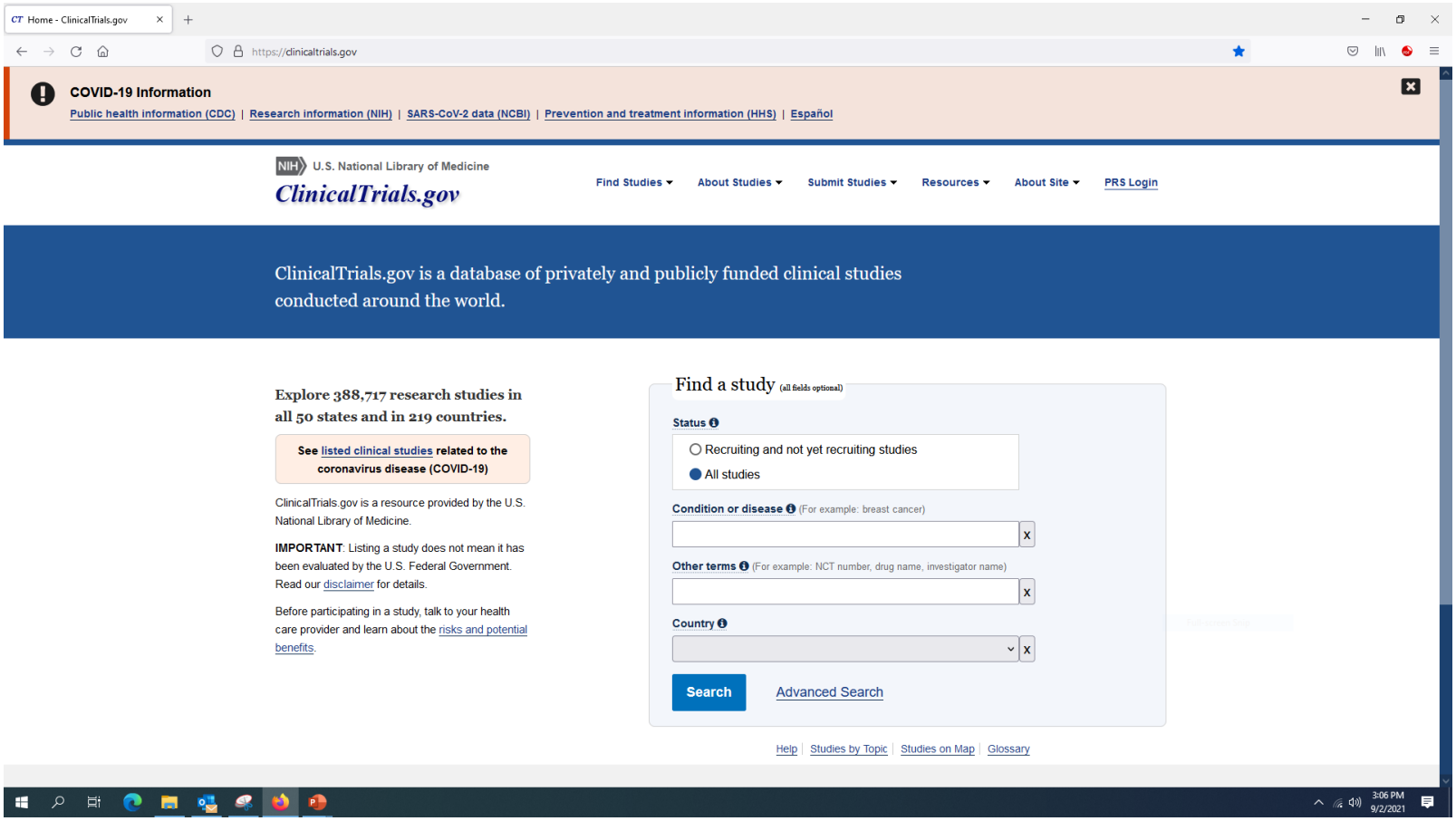
Physician-Offered/Not offered to patient

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**

Unger et al JNCI 2019

How to Find a Clinical Trial



Immunotherapy

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**

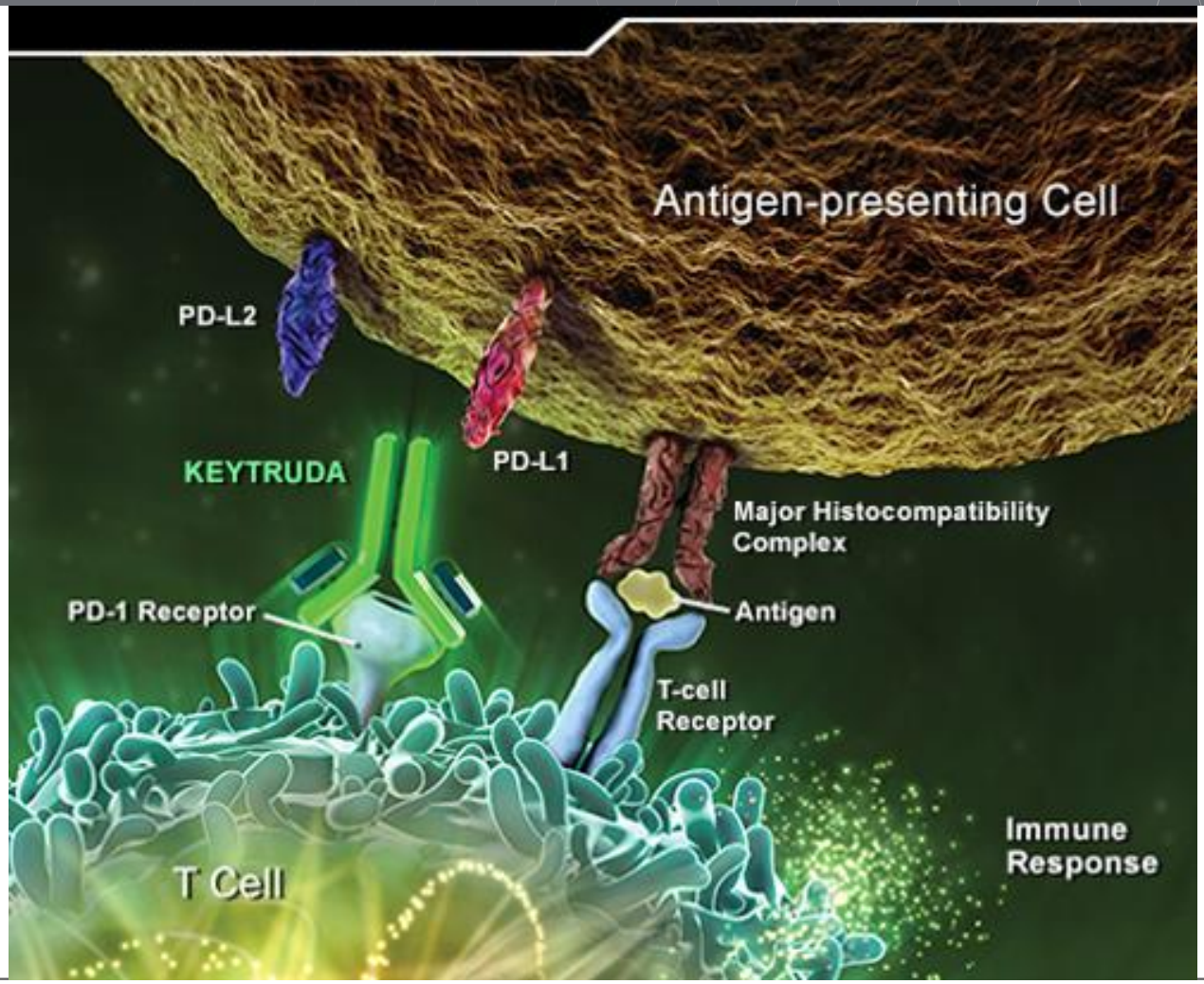
Vaccines

- **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 I Selected completed immunotherapy studies in soft-tissue sarcoma (STS)

Reference	Agent	Phase	Pts (*n*)	Indication	Response rate	Survival
Checkpoint inhibitors						
Maki *et al.*, 2013[19]	Ipilimumab	I	6	Advanced SyS	0 of 6	mOS: 8.75 months
Tawbi *et al.*, 2017[16]	Pembrolizumab	II		Selected STSs and bone sarcomas	18% in STS, 40% in UPS, 20% in LPS, 10% in SyS	mPFS: 18 weeks; OS: 49 weeks
D'Angelo *et al.*, 2018[21]	Nivolumab with or without ipilimumab	II	96	Metastatic STS	Nivolumab: 5%; Ipilimumab–nivolumab: 16%	mPFS: 4.1 months; OS: 14.3 months
Toulmonde *et al.*, 2018[26]	Pembrolizumab, cyclophosphamide	II	57	Advanced STS	Solitary fibrous tumour in 1 patient	NA
Wilky *et al.*, 2019[22]	Axitinib, pembrolizumab	II		ASPS and other STSs	25%, all STS patients; 50.4%, ASPS patients	3-Month PFS: 66%; in ASPS patients: 73%
Adoptive cell therapy						
Robbins *et al.*, 2011[27]	Adoptively transferred autologous T cells transduced with a T cell receptor directed against NY-ESO-1	I	6	Metastatic SyS expressing NY-ESO-1	4 of 6	NA
Vaccines						
Mahvi *et al.*, 2002[28]	Tumour cells treated with granulocyte macrophage colony–stimulating factor	I	16	Melanoma and sarcoma	1 of 16	NA
Dillman *et al.*, 2004[29]	Autologous tumour cell-line-derived vaccines	I/II	23	Recurrent or metastatic sarcoma	No objective response	10 Patients lived more than 1 year
Kawaguchi *et al.*, 2005[30]	Vaccination with SYT–SSX junction peptide	I	6	Metastatic SyS	0 of 6	NA
Finkelstein *et al.*, 2012[31]	Radiotherapy with intratumoural injection of dendritic cells	I/II	17	Neoadjuvant treatment in high-risk STS	9 of 17	1-Year PFS: 70.6%
Kawaguchi *et al.*, 2012[32]	SYT–SSX breakpoint peptide vaccines	I/II	21	Metastatic SyS	1 of 21 (stable disease: 6 of 21)	NA

Pts = patients; SyS = 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.

Ayodele O, Current Oncology 2020

Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial

Hussein A Tawbi, Melissa Burgess, Vanessa Bolejack, Brian A Van Tine, Scott M Schuetze, James Hu, Sandra D'Angelo, Steven Attia, Richard F Riedel, Dennis A Priebat, Sujana Movva, Lara E Davis, Scott H Okuno, Damon R Reed, John Crowley, Lisa H Butterfield, Ruth Salazar, Jaime Rodriguez-Canales, Alexander J Lazar, Ignacio I Wistuba, Laurence H Baker, Robert G Maki, Denise Reinke, Shreyaskumar Patel

	Complete response	Partial response	Stable disease	Progressive disease
Soft-tissue sarcomas (n=40)	1 (3%)	6 (15%)	15 (38%)	18 (45%)
Leiomyosarcoma (n=10)	0 (0%)	0 (0%)	6 (60%)	4 (40%)
Undifferentiated pleomorphic sarcoma (n=10)	1 (10%)	3 (30%)	3 (30%)	3 (30%)
Liposarcoma (n=10)	0 (0%)	2 (20%)	4 (40%)	4 (40%)
Synovial sarcoma (n=10)	0 (0%)	1 (10%)	2 (20%)	7 (70%)
Bone sarcomas (n=40)	0 (0%)	2 (5%)	9 (23%)	29 (73%)
Chondrosarcoma (n=5)	0 (0%)	1 (20%)	1 (20%)	3 (60%)
Ewing's sarcoma (n=13)	0 (0%)	0 (0%)	2 (15%)	11 (85%)
Osteosarcoma (n=22)	0 (0%)	1 (5%)	6 (27%)	15 (68%)

Data are n (%).

Table 2: Best response in 80 evaluable patients by sarcoma histological subtype

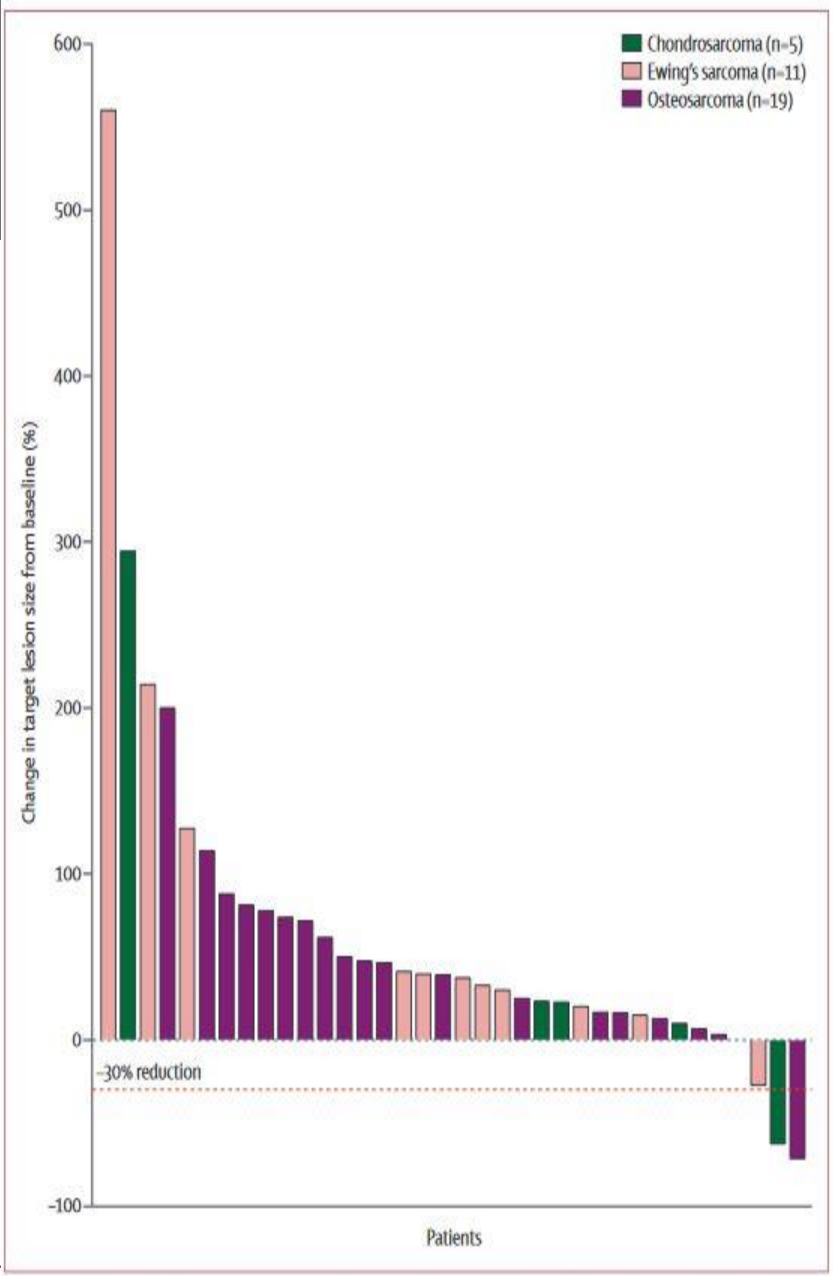


Figure 4: **Best percentage change from baseline in size of target lesions in patients with bone sarcoma**
Tumour sizes were calculated as the sum of target lesion diameters. Data for two patients with Ewing's sarcoma and three patients with osteosarcoma are not shown because they did not have a second scan.

Lancet Oncology
2017

Cedars Sinai

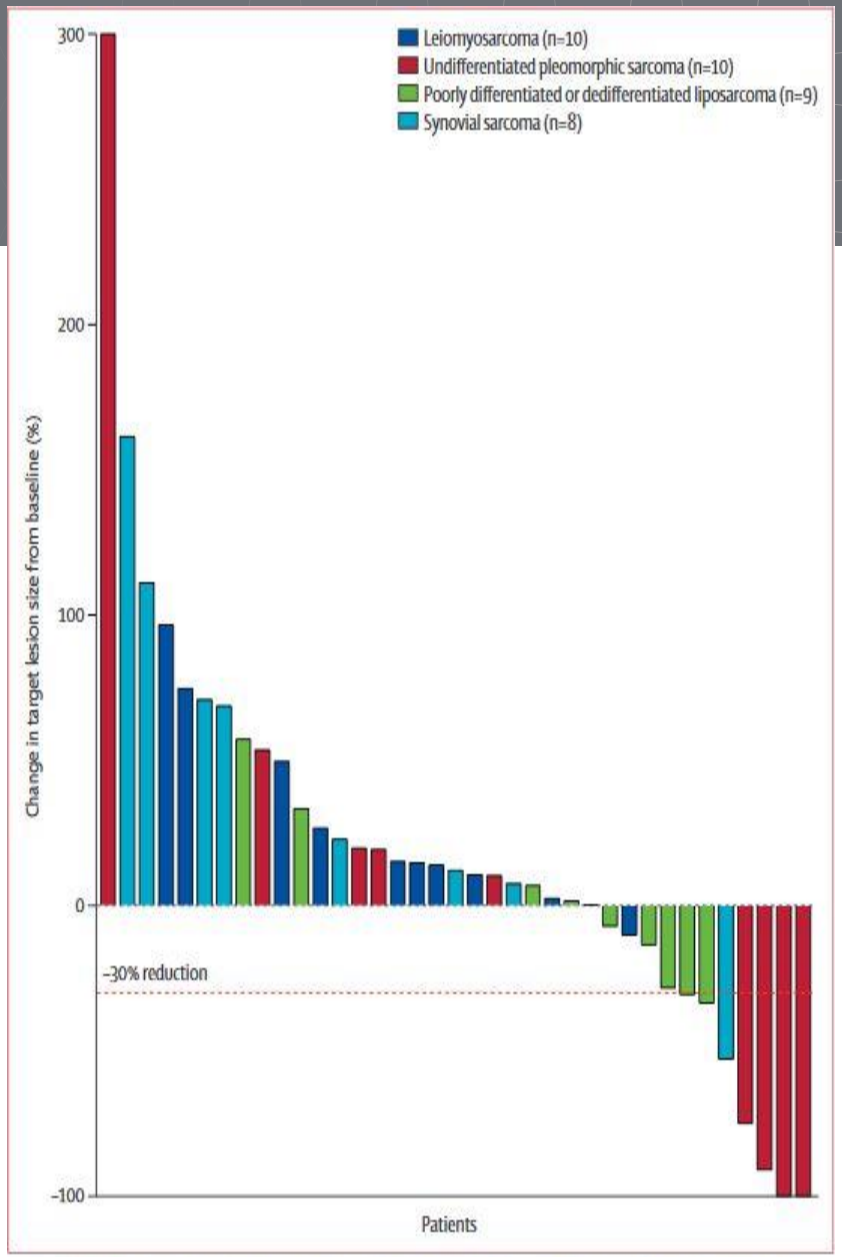


Figure 2: Best percentage change from baseline in size of target lesions in patients with soft-tissue sarcoma
Tumour sizes were calculated as the sum of target lesion diameters. Data for two patients with synovial sarcoma and one patient with liposarcoma are not shown because they did not have a second scan.

Lancet Oncology 2017

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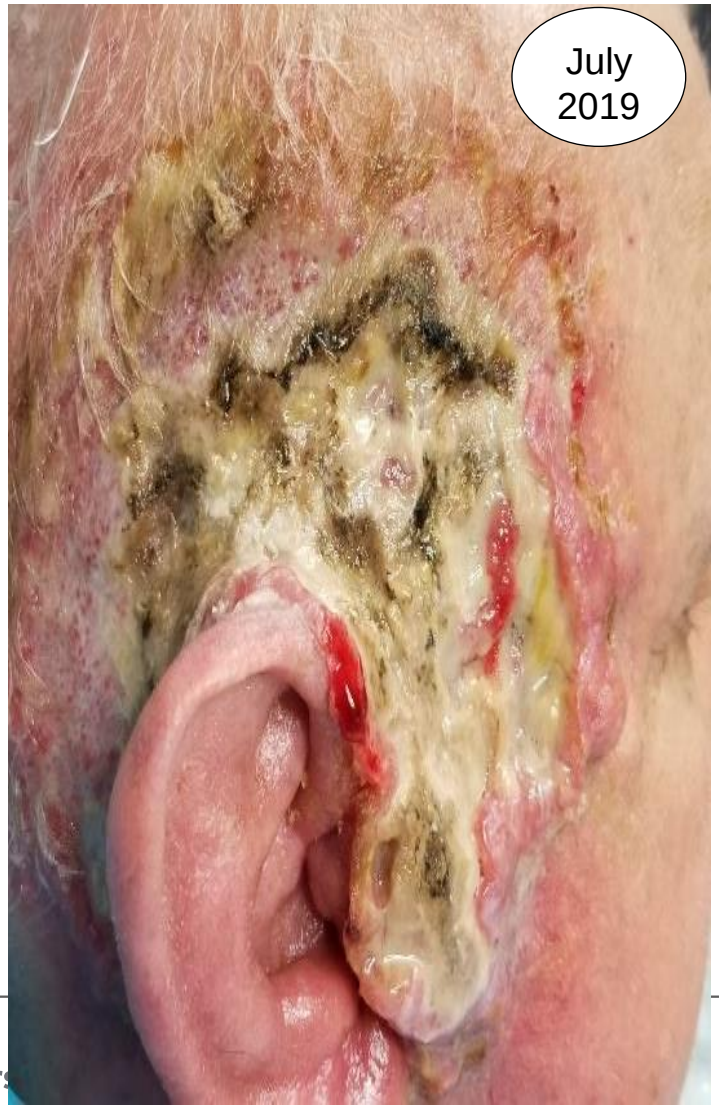
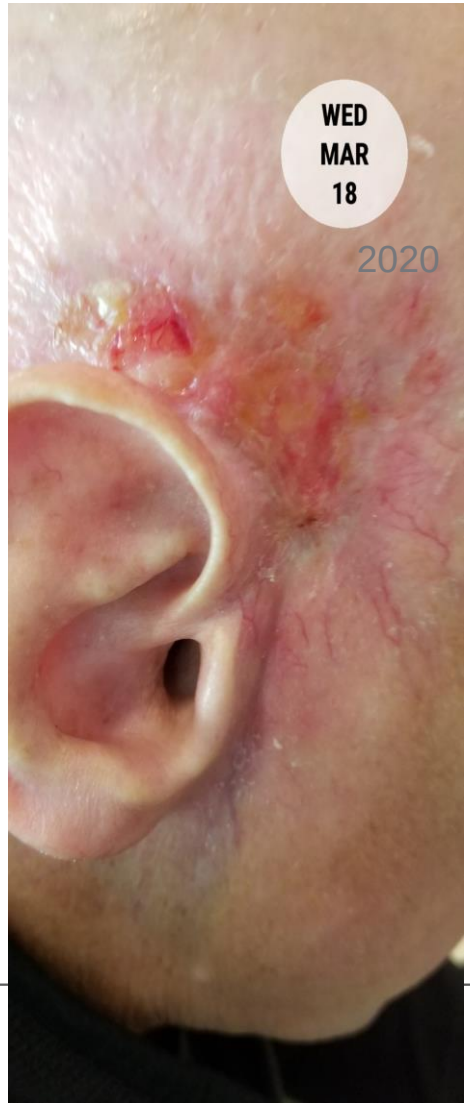
Immune Checkpoint Inhibitors Appear To Be Most Active in Cutaneous Angiosarcoma, Chordoma and Alveolar Soft Part Sarcoma

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 and Hyperprogression

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

Future of Immunotherapy for Sarcomas

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