



SARC : collaborations in defining the future treatment of sarcoma.

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WHAT IS SARCA?

- **Sarcoma Alliance for Research through Collaboration**
- Formed in 2003 at 5 major medical centres to facilitate the more effective completion of sarcoma clinical trials.
- In the USA, NIH and NCI effective in the management of common cancers
- Do not have necessary multidisciplinary level of collaboration required to achieve the desired outcome for sarcoma patients.

WHAT IS SARC?

Not for profit organisation based in Michigan

Funded by: Department of Energy
 Department of Defense
 pharmaceutical companies
 philanthropic donations

VISION

SARC seeks to engage resources to develop new therapeutic options that lead to improved outcomes for patients diagnosed with sarcoma.

MISSION



The mission of SARC is to:

- Provide the infrastructure and support to answer important clinical questions in an expeditious way.
- Collaborate to design cost effective and efficiently executed clinical trials
- Further the scientific knowledge regarding diagnosis and treatment of sarcoma
- Provide the most up-to-date information to physicians, patients, and caregivers

AIMS

- i) Timely recruitment to studies through collaboration
- ii) Conduct trials that build on concepts
- iii) Group resources to progress from I/II-III more quickly and seamlessly
- iv) Include younger patients
- v) Ensure biological end-points are a key component of studies

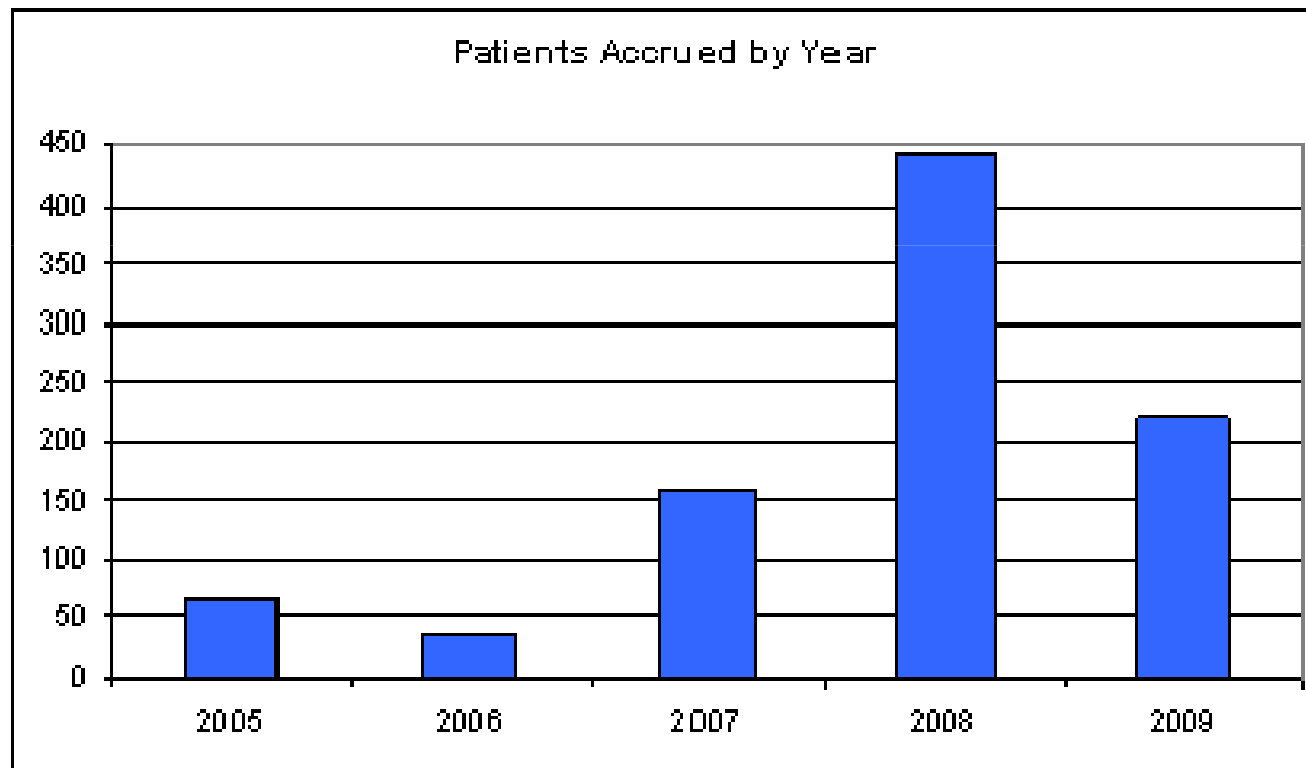
WHERE ARE THEY NOW? – 6 YEARS LATER

Activated 10 trials

Study	Phase	Protocol	Indication	Status
001	II	Phase II Trial of Imatinib Mesylate (Gleevec) in Patients with Soft Tissue and Bone Sarcomas: A Multi-Disciplinary Trial	Soft tissue and bone sarcoma	CLOSED
002	III	Phase III Randomized Trial of 120-minute infusion Gemcitabine v. 90-minute infusion Gemcitabine plus Docetaxel in unresectable Soft Tissue Sarcoma; A Multi-Disciplinary Trial of the North American Sarcoma Study Group of the Connective Tissue Oncology Society	Unresectable soft tissue sarcoma	CLOSED
003	II	SARC (Sarcoma Alliance for Research through Collaboration) Study: Phase II study of Sequential Gemcitabine Followed by Docetaxel for Recurrent Ewing's Sarcoma, Osteosarcoma, or Unresectable or Locally Recurrent Chondrosarcoma	Ewing's Sarcoma, Osteosarcoma and Chondrosarcoma	Closed to accrual
004		Study of a Short Course of Neoadjuvant Gleevec (Imatinib Mesylate) in Dermatofibrosarcoma Protuberans	Dermatofibrosarcoma protuberans	Closed to accrual
005	II	Adjuvant treatment of high risk leiomyosarcoma with gemcitabine/docetaxel, followed by doxorubicin; a phase II multi-center trial	Uterine leiomyosarcoma	Closed to accrual
006	II	Phase II Trial of Neoadjuvant Chemotherapy in Sporadic Neurofibromatosis Type 1 Associated High Grade Unresectable Malignant Peripheral Nerve Sheath Tumors	Sporadic and neurofibromatosis associated with Peripheral Nerve Sheath Tumors	OPEN
007	II	A Phase II Trial of Perifosine in Patient with Chemo-insensitive Sarcomas	Chemo-insensitive sarcomas	Closed to accrual
009	II	A Phase II Trial of Dasatinib in Advanced Sarcoma	Advanced sarcoma	OPEN
010	II	TBA	GIST	In development
011	II	A Phase II Multi-Arm Trial of R1507 IGF1R, a Recombinant Human Monoclonal Antibody for the treatment of patients with recurrent or refractory Ewing's sarcoma, and other Soft Tissue Sarcomas	Ewing's sarcoma, Osteosarcoma, synovial sarcoma, rhabdomyosarcoma and others	Open (Only accruing Ewing's patients)
012	II.5	A Randomized, Double-Blinded, Placebo-Controlled, Multi-Institutional, Phase II.5 Study of AZD0530, a Selective Src Kinase Inhibitor, in Patients with Recurrent Osteosarcoma Localized to the Lung	Osteosarcoma	Open

WHERE ARE THEY NOW? – 6 YEARS LATER

Recruited > 1000 patients



To
September
2009

HOW? SARC SITES IN THE USA-2009

SARC

47
centres
in USA



HOW? SARC SITES OUTSIDE USA - 2009

UK **4** **(Birmingham, Christie, RMH, UCH)**

France	5	Australia	1
Germany	5	Canada	1
Spain	3	Norway	1
Italy	2	Sweden	1
Belgium	1	Total	24

>80 new patients/year
>20 if paediatric centre
Members of CTOS
Dedicated to research

TIMELY RECRUITMENT - STUDY ACCRUAL

Study	Activation	No. patients	Accrual/ month	Time to completion (yrs)
SARC001	11/2001	185	5.7	3.5
SARC002	1/2003	122	3.1	3.3
SARC003	5/2005	45	1.1	4
SARC004	12/2006	15	0.4	3.6
SARC005	2/2006	45	1.3	3
SARC006	12/2005	74	0.4	14
SARC007	11/2006	111	4.5	1.3*
SARC009	5/2007	520	11.4	3.4
SARC011	12/2007	312	17.2	1.5*
SARC012	4/2009	88	0.4	17

SARC STUDIES – THEMES - Chemotherapy

VOLUME 25 - NUMBER 19 - JULY 1 2007

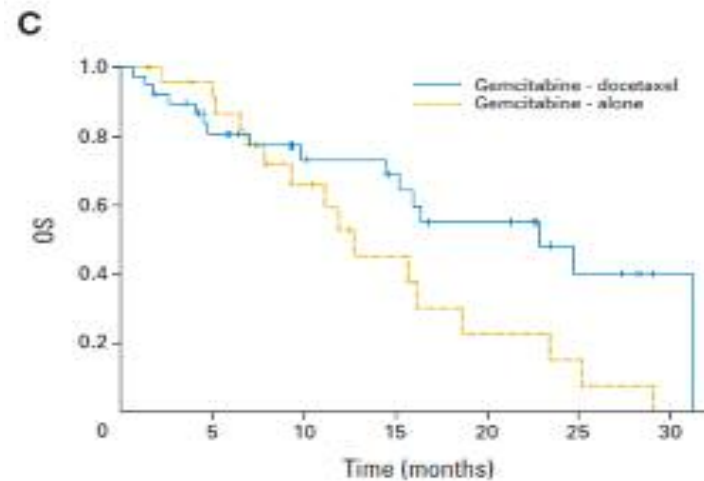
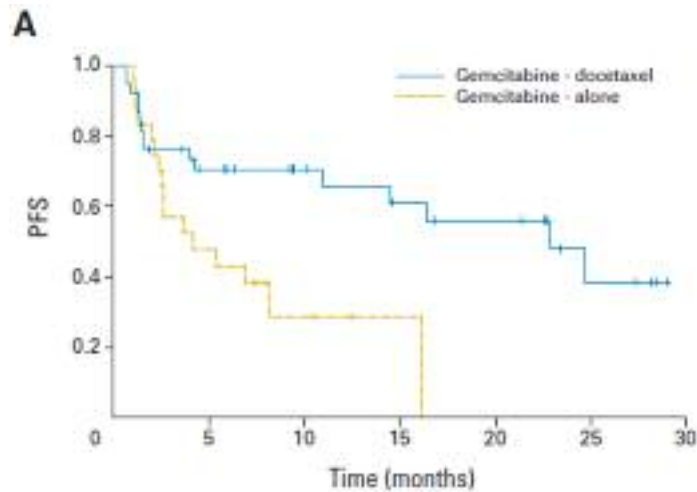
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

SARC002

Randomized Phase II Study of Gemcitabine and Docetaxel Compared With Gemcitabine Alone in Patients With Metastatic Soft Tissue Sarcomas: Results of Sarcoma Alliance for Research Through Collaboration Study 002

Robert G. Maki, J. Kyle Wathen, Shreyaskumar R. Patel, Dennis A. Priebat, Scott H. Okano, Brian Samuels, Michael Fanucchi, David C. Harmon, Scott M. Schuetz, Denise Reinke, Peter F. Thall, Robert S. Benjamin, Laurence H. Baker, and Martee L. Hensley



Bayesian Adaptive Randomisation

Reduced number of patients randomised to inferior treatment.

SARC STUDIES – THEMES - Chemotherapy

Gemcitabine / Docetaxel

SARC003. Phase II study of gemcitabine / docetaxel in patients with recurrent Ewing's sarcoma, osteosarcoma or chondrosarcoma.

→ not fully reported. OS arm closed due to lack of activity

SARC005. Adjuvant gemcitabine / docetaxel and doxorubicin in patients with high risk uterine leiomyosarcoma. → not reported

SARC006. Phase 2 trial of neo-adjuvant chemotherapy sporadic vs. NF-associated MPNST.

TARGETED AGENTS - IMATINIB

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

SARC001

Phase II Multicenter Trial of Imatinib in 10 Histologic Subtypes of Sarcoma Using a Bayesian Hierarchical Statistical Model

Rashmi Chugh, J. Kyle Wathen, Robert G. Maki, Robert S. Benjamin, Shreyaskumar R. Patel, Paul A. Myers, Dennis A. Priebe, Denise K. Reinke, Dafydd G. Thomas, Mary L. Keohan, Brian L. Samuels, and Laurence H. Baker

Table 4. Posterior Estimates Based on the BHM Used for Monitoring the Trial

Subtype	Observed Response (%)	Estimated Response Based on BHM (%)	Probability of Response Rate at Least the 30% Target
Angiosarcoma	13.3	12.4	.029
Ewing	0.0	3.3	.0009
Fibrosarcoma	8.3	9.1	.018
Leiomyosarcoma	21.4	20.1	.095
Liposarcoma	24.1	21.9	.134
MFH	10.3	10.4	.002
Osteosarcoma	19.2	18.0	.060
MPNST	20.0	14.0	.095
Rhabdomyosarcoma	0.0	9.9	.083
Synovial	15.0	13.4	.021

Abbreviations: BHM, Bayesian hierarchical model; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral-nerve sheath tumor.

185 patients.

No activity in any histological subtypes

TARGETED AGENTS - IMATINIB

- **SARC004:** short-course neo-adjuvant imatinib in patients with dermatofibrosarcoma protuberans (DFSP).
- **SARC019:** phase III of dose escalation vs. no dose escalation in metastatic GIST patients with low trough levels of imatinib

TARGETED AGENTS–SRC KINASE INHIBITORS

- **SARC009** – a Phase II Trial of dasatinib (inhibits Src, PDGFR, C-KIT, BCR-ABL and ephrin receptor kinases) in advanced sarcoma.
- 330 patients. Responses seen in “MFH” and osteosarcoma. Dose-reductions required for toxicity.
- **SARC012**- randomised, placebo-controlled controlled phase II study of AZD00530 in patients with recurrent osteosarcoma localised to the lung.
 - translational end-points

TARGETED AGENTS- ANTI- IGFR ANTIBODY - R1507

SARC011 - R1507 in patients with recurrent, metastatic Ewing's sarcoma, osteosarcoma and other sarcomas

Collaboration with Roche/Genentech on the basis of results of Phase I study – 2007

“We are very encouraged by [these] early results with R1507 in patients with refractory Ewing's sarcoma,” said Kapil Dhingra, MD, Head, Oncology Disease Biology Area at Roche. “As a result, **we have given this program a very high priority** as we believe this molecule has the potential to be very beneficial in treating patients with sarcoma as well as a variety of other solid tumors.”

First global collaboration. Total sites: 47 : Europe = 22 (UK 4),

Recruited 310 patients in 18 months, 17 patients / month

Multiple treatment cohorts, expanded cohorts

FURTHER STUDIES WITH R1507 IN DEVELOPMENT

- **SARC013** - Randomised phase III combination study of topotecan / cyclophosphamide +/- R1507 in relapsed Ewing's sarcoma.
- **SARC014**- Phase I study of R1507 in combination with rapamycin in patients with sarcoma
- **SARC015** – Phase II study of R1507 in wild-type GIST including children
- **22/12/2009** –Roche / Genentech decided to halt development of R1507
- **SARC011** not completed and no further development

WHAT WERE THE LESSONS LEARNT?

Attempted to select the best partner based on the strategy and priority set by potential partners.

SARC led the scientific development / basis of the concept and SARC011 was run as an “Investigator-initiated study.”

BUT

No control of financial climate and potential re-structuring.

Therefore, will be an element of risk

Had a number of further protocols in development, and therefore nearly half of the development portfolio was lost.

Demonstrated ability to run global studies with timely recruitment

FURTHER STUDIES



- Other novel agents:
- SARC016: mTOR inhibitor (everolimus) and bevacizumab in patients with MPNST
- SARC017: Phase I/II SF1126 (PI3K inhibitor) and imatinib in GIST.
- SARC018: Pilot multi-centre study of pre-operative RT and surgery in patients with high-risk desmoid tumours.

MEETING THE NEEDS OF YOUNG PEOPLE

- SARC001 >10 years
- SARC002 > 10 years
- SARC003 > 10 years
- SARC004 > 18 years DFSP
- SARC005 > 18 years ut. leiomyosarcoma
- SARC006 no lower or upper age limit
- SARC007 > 13 years
- SARC009 > 13 years
- SARC011 >10 years
- SARC012 > 14 years

THE FUTURE - INCREASING COLLABORATIONS

- **COG**
- **NF-1 consortium**

SARC016: phase II study mTOR inhibitor (everolimus) and bevacizumab in patients with sporadic and NF-1 assoc refractory MPNST

- **EORTC**

First collaborative study

EORTC 62091/SARC020 Phase IIb/III study comparing trabectedin 3hr or 24 hr infusion with doxorubicin in metastatic STS.

FUNDING OPPORTUNITIES

Provide other funding opportunities

- **New concept studies** – funding and support available to conduct and adopt trials. Four submitted since first call in March 2009, but at present only US-based studies.
- **SARC career development award**
- “support clinician-scientists working in sarcoma as they begin their careers as independent clinical researchers”.
 - \$300,000 over 3 years
 - since 2009.
 - 2 awards / year

CONCLUSIONS

- SARC dedicated to clinical sarcoma research
- Infrastructure to conduct trials in a timely fashion
- Increasing the number of sites
- Increasing global collaborations
- Increasing collaboration with other organisations
- Also aims to focus on translational endpoints
- Helping to define treatment in the future
- Provides other funding opportunities for research

ACKNOWLEDGEMENTS

- Denise Reinke – President of SARC
- Larry Baker – Chairman of the Board
- www.sarctrials.org

