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The Angiosarcoma Project: enabling genomic and clinical discoveries in a rare cancer through patient-partnered research

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Despite rare cancers accounting for 25% of adult tumors[1], they are difficult to study due to the low disease incidence and geographically dispersed patient populations, which has resulted in significant unmet clinical needs for patients with rare cancers. We assessed whether a patient-partnered research approach using online engagement can overcome these challenges, focusing on angiosarcoma, a sarcoma with an annual incidence of 300 cases in the United States. Here we describe the development of the Angiosarcoma Project (ASCproject), an initiative enabling US and Canadian patients to remotely share their clinical information and biospecimens for research. The project generates and publicly releases clinically annotated genomic data on tumor and germline specimens on an ongoing basis. Over 18 months, 338 patients registered for the ASCproject, which comprises a large proportion of all patients with angiosarcoma. Whole-exome sequencing (WES) of 47 tumors revealed recurrently mutated genes that included *KDR*, *TP53*, and *PIK3CA*. *PIK3CA*-activating mutations were observed predominantly in primary breast angiosarcoma, which suggested a therapeutic rationale. Angiosarcoma of the head, neck, face and scalp (HNFS) was associated with a high tumor mutation burden (TMB) and a dominant ultraviolet damage mutational signature, which suggested that for the subset of patients with angiosarcoma of HNFS, ultraviolet damage may be a causative factor and that immune checkpoint inhibition may be beneficial. Medical record review revealed that two patients with HNFS angiosarcoma had received off-label therapeutic use of antibody to the programmed death-1 protein (anti-PD-1) and had experienced exceptional responses, which highlights immune checkpoint inhibition as a therapeutic avenue for HNFS angiosarcoma. This patient-partnered approach has catalyzed an opportunity to discover the etiology and potential therapies for patients with angiosarcoma. Collectively, this proof-of-concept study demonstrates that empowering patients to directly participate in research can overcome barriers in rare diseases and can enable discoveries.

Owing to the low disease incidence, patients with rare cancers are often treated at disparate institutions distributed across the country, that range from tertiary medical centers to community hospitals. This poses barriers to large-scale scientific studies that are urgently needed to understand the biology of rare cancers and to develop better treatments[1]. We hypothesized that the challenges of rare cancer research could be addressed if patients are engaged directly and empowered to share their samples, their data, and their experiences. In principle, a patient-partnered approach that harnesses the power of social media and patient networks and that enables patients to participate remotely, irrespective of geography, could overcome the barriers of low patient numbers that are seen at any single institution; this approach could be used to aggregate a large number of patients with rare cancers from numerous institutions in a unified clinicogenomic study, thereby rapidly yielding discoveries.

We aimed to test this patient-partnered research approach in angiosarcoma, a disease that represents just 1–2% of soft tissue sarcomas, which in turn comprise less than 1% of adult malignancies[2,3]. The prognosis for angiosarcoma is poor, with a reported 5-year disease-specific survival rate of 38% (ref. [2]). Despite small genomic studies of angiosarcoma reported so far[4–10], the majority of angiosarcoma have no known genomic, environmental, or iatrogenic etiology, and effective therapies for most patients with angiosarcoma are lacking.

We worked closely with patients and patient advocates to develop a website (https://ascproject.org) that allows patients with angiosarcoma who live anywhere in the United States and Canada to register for the ASCproject (Fig. 1a). Patients and loved ones in the angiosarcoma community were deeply involved in all aspects of the project design, implementation, testing, and refinement, including all elements of the study website from images to consent

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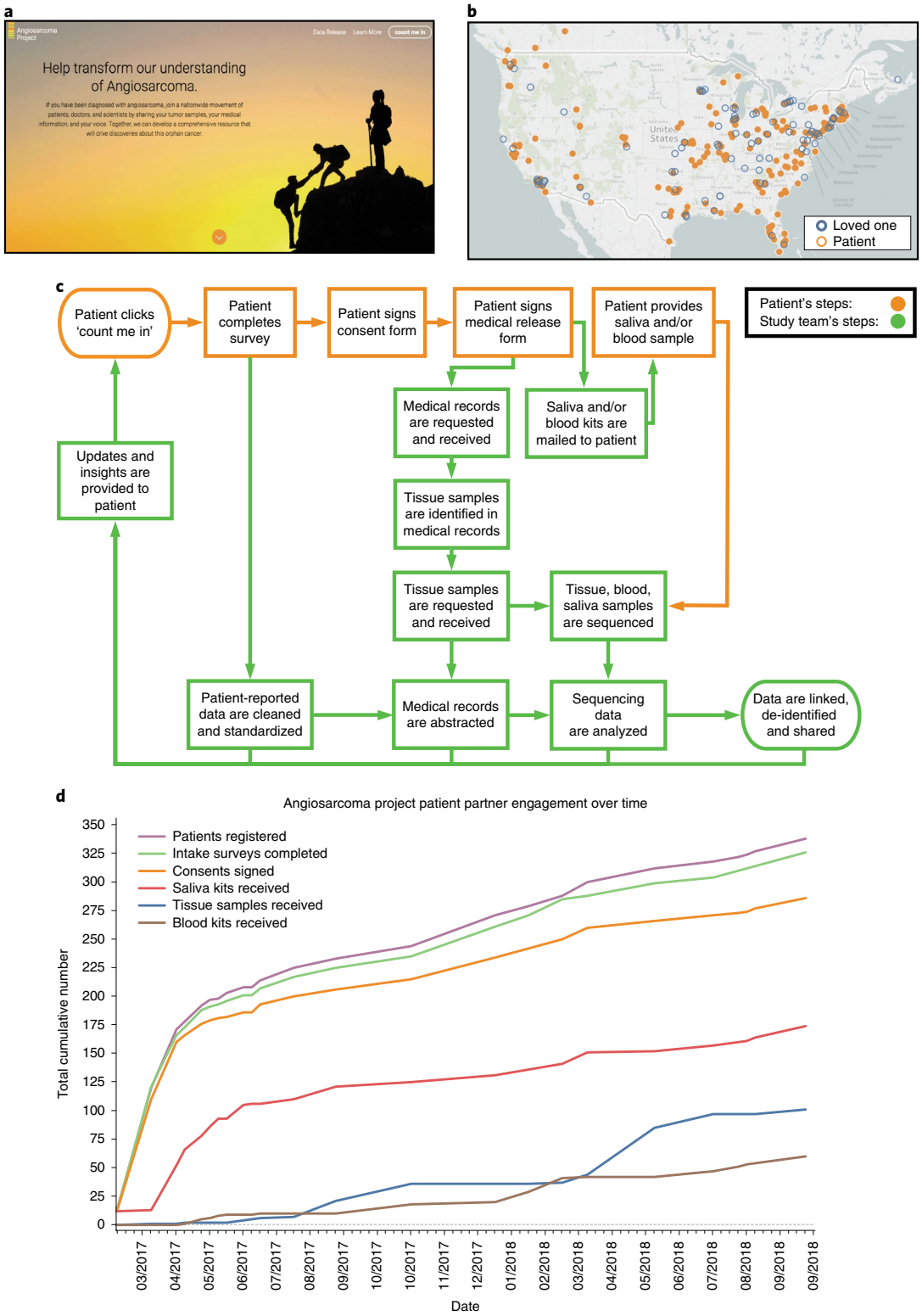

Fig. 1 | Building a patient-partnered project in angiosarcoma. a, Homepage of the ASCproject.org website, which shows images and text designed with input from patients with angiosarcoma. To begin the project enrollment process, patients click the 'count me in' button seen in the upper right corner. **b**, Map of the United States and Canada showing geographical locations of patients (solid orange circles) and loved ones (open blue circles) who registered for the ASCproject between 1 January 2017 and 30 September 2018. Map generated in Tableau using https://www.openstreetmap.org contributors, https://www.opendatacommons.org and https://creativecommons.org. **c**, Schematic detailing the process of the ASCproject (orange boxes indicate steps taken by patients; green boxes indicate steps taken by study team members). **d**, Plot depicting the cumulative totals of patient-driven aspects of the ASCproject between March 2017 and September 2018, which includes numbers of patients registering for the ASCproject (purple), patient intake surveys completed (green), patient consent forms signed (orange), and receipt at the Broad Institute of saliva kits (red), angiosarcoma tumor tissue samples (blue) and blood kits (brown). Fifteen patients with angiosarcoma served as beta testers of the website before the public launch of the ASCproject in March 2017, resulting in non-zero values at 1 March 2017.

language (Extended Data Figs. 1–3 and Supplementary Table 1; see Supplementary Methods). Patients with angiosarcoma joined the ASCproject rapidly after its launch; 120 patients registered in the first month and a total of 338 patients registered within 18 months (Fig. 1b). This represents not only a large proportion of people living with this disease in the United States but also a substantially increased pace of enrollment compared to that of previous efforts (with the largest previous angiosarcoma study having collected clinical data from 222 patients treated over 14 years) (ref. [2]). Online consent for the ASCproject allowed for acquisition of medical records and biological samples (tumor, saliva and blood), analysis of WES on tumor and germline DNA, and enabled de-identified patient-reported, clinical, and genomic data to be shared on public databases (Fig. 1c,d). Patients continued to be engaged throughout the ASCproject and were provided with regular study updates (Fig. 1c).

The study is ongoing, but the following analyses were conducted with the 227 patients who had fully consented as of 30 September 2018 (Fig. 1d). These 227 patients received care for angiosarcoma at 340 different clinical institutions, including 289 institutions that were reported only once by any given participant (Extended Data Fig. 4a). This demonstrates the importance of online platforms to overcome the geographic isolation that has traditionally inhibited large-scale studies of patients with rare cancers.

Patients self-reported demographic information and sites of primary angiosarcoma, as well as other angiosarcoma and prior cancer information through an intake survey (Fig. 2, Extended Data Fig. 4b,c and Supplementary Tables 2,3). Patients who joined the ASCproject ranged from newly diagnosed patients to long-term survivors, and the elapsed time between primary angiosarcoma diagnosis and ASCproject enrollment ranged from 5 days to 41 years (Fig. 2b).

We were able to acquire medical records and tumor samples from geographically dispersed patients and institutions (Extended Data Fig. 5). WES was performed on 70 tumor samples that study staff obtained. Forty-seven samples from 36 patients were used for subsequent genomic analysis after assessment of sufficient tumor purity (≥10%) and confirmation as angiosarcoma by centralized pathology review (Extended Data Fig. 5; see Supplementary Methods). Apart from these considerations, there were no additional selection criteria for these 47 samples. Characteristics of the 36 patients whose samples were sequenced are shown in Extended Data Fig. 6. Abstraction of medical record data (Supplementary Table 4) and histological evaluation were used to classify these tumors into eight subclassifications of angiosarcoma (see Supplementary Methods). To our knowledge, this is the largest reported cohort of angiosarcoma samples that have undergone WES.

We found that 30 genes were recurrently altered in these 47 samples (determined by somatic alteration frequency; see Supplementary Methods). These include genes that were previously reported as altered in angiosarcoma[6,7,10–12], as well as several genes that have not been reported previously to be mutated in angiosarcoma, such as *PIK3CA*, *GRIN2A*, and *NOTCH2* (Fig. 3a). Two genes were mutated at a rate that was significantly higher than expected by chance given background mutational processes (as identified by MutSig2CV software[13]; see Supplementary Methods): *TP53* (25%; 9 out of 36 patients) and *KDR* (22%; 8 out of 36 patients) (Extended

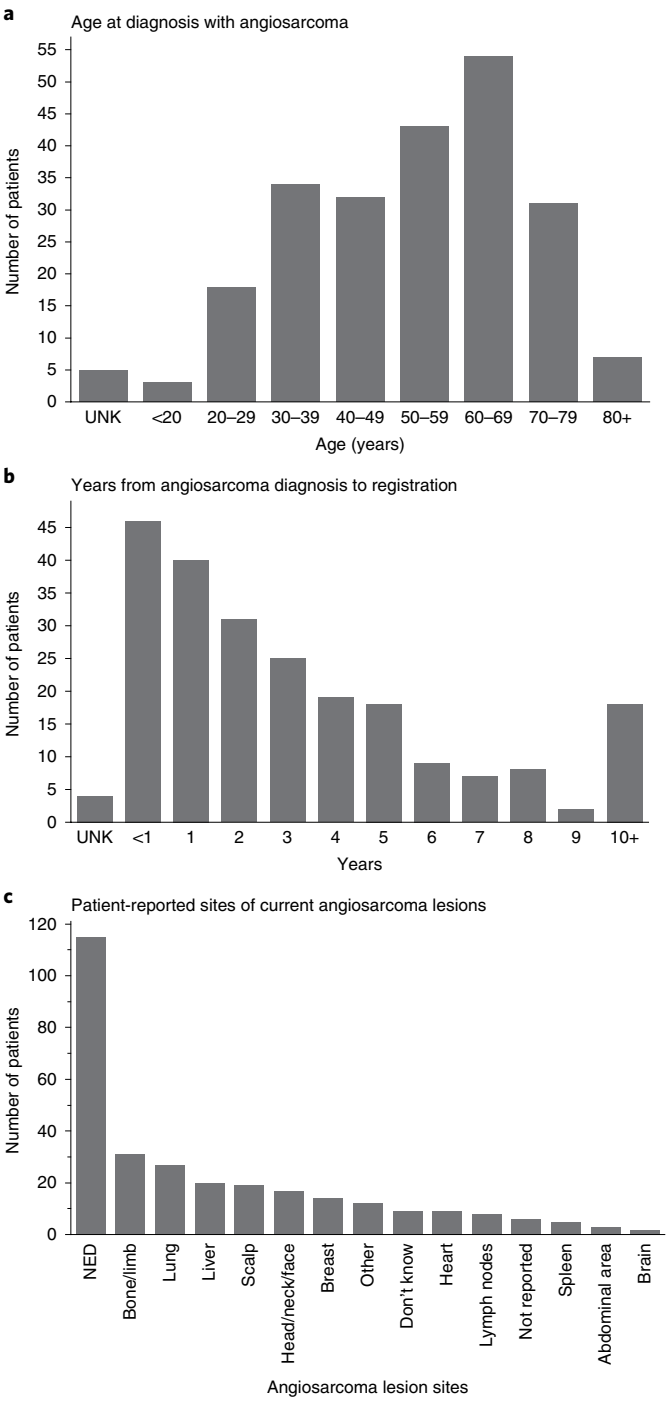

Fig. 2 | Patient-reported data in the Angiosarcoma Project. Patients first complete an intake survey during the ASCproject registration process. Surveys completed by the 227 patients from the United States and Canada who consented for the ASCproject as of 30 September 2018 were analyzed. **a**, Bar chart showing the age in years of patients at initial diagnosis with angiosarcoma (mean of 222 patients, 53.1 years). These values were calculated from patient-provided date of birth and date of initial angiosarcoma diagnosis. If insufficient information was provided to calculate this value, patient age was classified as 'Unknown' (5 patients). **b**, Bar chart showing the years elapsed between initial diagnosis of patients with angiosarcoma and registration of patients in the ASCproject (mean of 223 patients, 3.6 years). These values were calculated from the date of project registration and the patient-provided date of initial angiosarcoma diagnosis. If insufficient information was provided to calculate this value, it was classified as 'Unknown' (4 patients). **c**, Bar chart showing the patient-reported location of angiosarcoma at the time of last intake survey completion. An option was provided for patients to report no evidence of disease (NED). Patients with more than one location of angiosarcoma were able to provide more than one site. Nine patients responded 'Don't know', and six patients did not respond to this question ('Not reported'). UNK, unknown.

Data Fig. 7). Moreover, mutations in these two genes were also mutually exclusive ($P=0.02$, Fisher's exact test), with 89% (8 out of 9) of *KDR* missense mutations observed in primary breast angiosarcoma samples and 82% (9 out of 11) of *TP53* missense mutations detected in angiosarcoma samples that were not primary breast angiosarcoma (Fig. 3a and Extended Data Fig. 7).

PIK3CA was one of the most frequently mutated genes in this cohort (21%; 10 out of 47 samples) (Fig. 3a). Although alterations in the PI3K pathway have been identified in a previous angiosarcoma study[14], mutations in the *PIK3CA* gene itself have not been reported previously in angiosarcoma to our knowledge. Nine out of the ten *PIK3CA* alterations were found in primary breast angiosarcoma samples, and this angiosarcoma subclassification was significantly enriched for *PIK3CA* mutations compared to other subclassifications (9 out of 18 primary breast angiosarcoma samples versus 1 out of 29 angiosarcoma samples that were not primary breast angiosarcoma; $P=0.0003$, Fisher's exact test) (Fig. 3a).

Intriguingly, none of the eight unique *PIK3CA* mutations that were observed in this study were at the canonical *PIK3CA* hotspot residues Glu545 or His1047 (ref. [15]) (Fig. 3b). Instead, these *PIK3CA* mutations were located in two distinct clusters on the protein structure (Fig. 3c), which correspond to regions enriched with activating somatic mutations[16]. Indeed, most of the *PIK3CA* mutations in our angiosarcoma cohort have been described previously as hotspot mutations in other cancers, and have been shown to be activating in vitro[17–19] (Supplementary Table 5). Moreover, CRISPR experiments in cancer cell lines (https://depmap.org) demonstrated that lines that harbor some of these *PIK3CA* mutations (Arg88Gln, Pro124Leu, and Gly914Arg) were significantly more dependent on *PIK3CA* than were lines with wild type *PIK3CA* (Extended Data Fig. 8). Collectively, these data strongly suggest that the *PIK3CA* mutations that were detected in this angiosarcoma cohort are likely to be activating and are therefore sensitive to PI3Kα inhibition[20–22].

PIK3CA alterations occur more frequently in breast adenocarcinoma (34.5%) than in other cancer types (>10%) (refs. [23,24]). The fact that different types of activating PI3K mutations are found in breast malignancies with different lineages (angiosarcoma and adenocarcinoma), raises the intriguing possibility that the site of tumor origin (breast), independent of tumor lineage, may be permissive for PI3K pathway activation and may aid tumor formation within breast tissue, perhaps due to interaction with the breast microenvironment. Of clinical importance, these observations suggest that PI3Kα inhibitors, one of which was recently approved for the treatment of *PIK3CA*-mutant advanced breast adenocarcinoma[20], may be useful as a novel targeted therapeutic intervention for these patients with primary breast angiosarcoma.

We next quantified the TMB for all 47 angiosarcoma samples. Although the median TMB in the full cohort was 3.3 mutations per megabase (Mb), HNFS angiosarcoma samples showed a significantly higher median TMB than all other angiosarcoma subclassifications (20.7 mutations per Mb for HNFS versus 2.8 mutations per Mb for non-HNFS; $P=1.10\times10^{-5}$, two-sided Wilcoxon rank sum test). Moreover, 9 of the 10 samples with high TMB (≥10 mutations per Mb) were HNFS angiosarcoma (Fig. 3d). Using mutational signature analysis to understand the possible origins of tumor hypermutation, we found that all nine of these HNFS samples with high TMB had a dominant mutational signature representing damage from ultraviolet light (COSMIC Signature 7) (ref. [25]) (Fig. 3e and Extended Data Fig. 7d). The single sample with a high TMB that did not have a dominant ultraviolet light exposure mutational signature was from a patient with cutaneous radiation-associated angiosarcoma (C-RAAS) of the breast who also has Lynch syndrome (Fig. 3d,e and Extended Data Fig. 7d). Our findings suggest that these HNFS angiosarcoma tumors may have resulted from a high TMB caused by ultraviolet damage due to sun exposure (Fig. 3e and Extended Data Fig. 7d). Indeed, 10 out of the 12 HNFS angiosarcoma tumor samples in this study showed a dominant ultraviolet light exposure mutational signature, whereas none of the other 35 non-HNFS tumor samples harbored this as a dominant mutational signature ($P=1.27\times10^{-8}$, Fisher's exact test) (Fig. 3e and Extended Data Fig. 7d). Previous studies have reported a variety of mutational signatures in sarcoma samples[26–28], including evidence of ultraviolet damage in some superficial sarcoma samples and sarcomas with a high TMB[27–29]; this study identifies an ultraviolet damage mutational signature in angiosarcoma, and particularly in patients with angiosarcoma of HNFS. The fact that a high TMB and a concomitant dominant mutational signature of ultraviolet light exposure occurs uniquely in HNFS angiosarcoma suggests a common etiological and genomic basis for HNFS angiosarcoma, which is a subtype that accounts for nearly 60% of angiosarcoma cases[30,31].

As a high TMB has been reported as a possible biomarker for response to immune checkpoint inhibition[32–34], we reasoned that patients with HNFS angiosarcoma and a high TMB might respond particularly well to immune checkpoint inhibitors (ICIs). Medical record abstraction of radiation and all systemic treatments for angiosarcoma that were received by the sequenced cohort (Fig. 4a and Extended Data Fig. 9) revealed that three out of ten patients with HNFS angiosarcoma had received off-label therapeutic use of anti-PD-1 (Fig. 4 and Supplementary Table 6). Two of those patients with HNFS had metastatic angiosarcoma that was refractory to standard therapies, and demonstrated an exceptional and durable response to pembrolizumab. After they received several prior therapies for angiosarcoma that failed, each of these patients has remained disease-free for more than 2 years after discontinuation of pembrolizumab and has not received any subsequent therapy for angiosarcoma (Fig. 4b and Supplementary Table 7). Notably, the tumors of these two patients had a high TMB (78.5 and 138.9 mutations per Mb, respectively; Figs. 3d,4b) and a dominant ultraviolet light exposure mutational signature (Fig. 3e). The third patient with HNFS angiosarcoma received a single dose of anti-PD-1 immunotherapy, which was stopped because of side effects; this patient went on to receive other therapies, none of which resulted in any durable response (Supplementary Table 6).

By contrast, 3 of the 26 patients with non-HNFS angiosarcoma (primary breast, cardiac and lung) received off-label use of an anti-PD-1 ICI treatment without clinical benefit (Supplementary Table 6). Tumor samples from these 3 patients with non-HNFS angiosarcoma had a TMB of less than 5 mutations per Mb and did not demonstrate a dominant ultraviolet light exposure mutational signature (Supplementary Table 6). These data support the hypothesis that, as in melanoma[35–38], nearly all patients with HNFS angiosarcoma have an ultraviolet damage-mediated high TMB and might benefit from ICI-directed immunotherapy. Public release of these early results from the ASCproject have helped to catalyze the sarcoma community to design clinical trials focused on studies of the impact of ICI immunotherapy in HNFS angiosarcoma.

In summary, we illustrate that a patient-partnered approach that leverages social media (Extended Data Fig. 10) can circumvent the challenges experienced in the study of a rare cancer that are normally encountered through traditional research models, and can enable research in the extremely rare cancer, angiosarcoma. This approach expands and builds on approaches that were used in prior efforts to collect data and blood samples remotely from patients with cancer across the United States using the internet, including in myeloproliferative disease[39] and lung cancer[40]. Within only 18 months of its launch, the ASCproject accrued the largest prospective angiosarcoma cohort that has been reported to date and whose care for angiosarcoma spanned 340 different institutions. This underscores how this unique research approach can more fully capture and integrate new types of valuable data, including off-label use of therapies, that better reflect the varied treatment protocols across different parts of the country, ranging from community hospitals

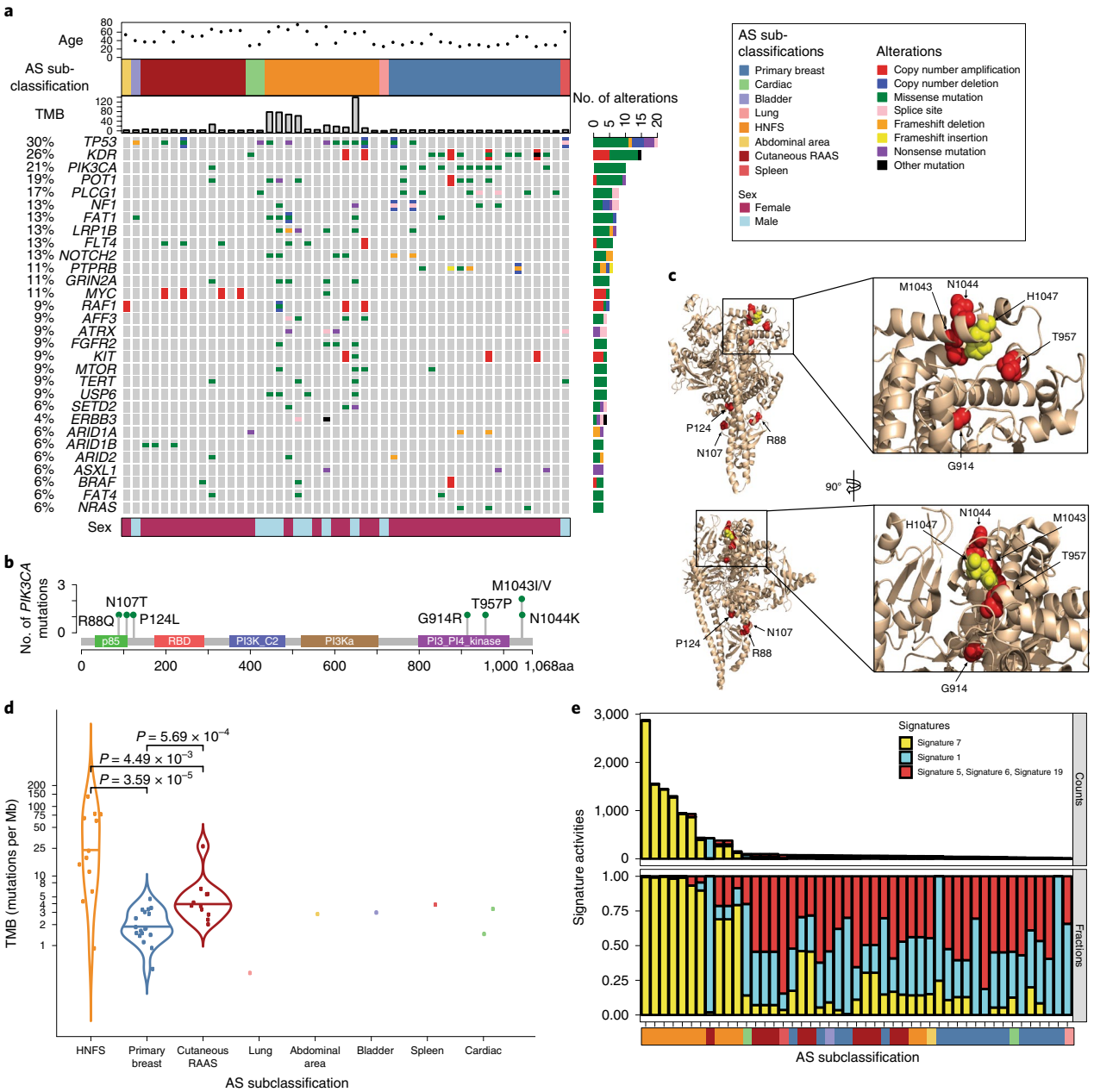

Fig. 3 | Genomic landscape of angiosarcoma reveals distinct molecular patterns. a, Co-mutation plot showing somatic alterations and copy number changes in frequently altered genes and other angiosarcoma-associated genes across the cohort of 47 tumor samples from 36 patients with angiosarcoma. Information for each sample is shown in the upper panels, including age at angiosarcoma diagnosis of the patient from whom the sample is derived (top), categorization of each sample to the eight subclassifications of angiosarcoma (middle), and the TMB (bottom). The sex of the patient is indicated in the lower panel of the plot (see the key to the right of panel **a**, which also lists the subclassifications and alteration types). **b**, Diagram indicating the location and count of mutations occurring in *PIK3CA* in the angiosarcoma cohort. **c**, Crystal structure of p110alpha protein (PDB ID: 3HHM) in wheat cartoon, with red spheres indicating residues found to be mutated in angiosarcoma tumor samples and the H1047 canonical mutation (yellow spheres). A closer view of the structure with mutations labeled in the regulatory arch region shows a cluster of mutations proximal to H1047 (right hand side). A 90° rotation of this structure is shown in the lower panel. **d**, Violin plot showing the distribution of TMB (range: 0.4–138.9) across tumor samples stratified by the 8 different subclassifications of angiosarcoma. Tumors from the HNFS subclassification exhibit the highest median TMB of 20.7 mutations per Mb ($n=12$ tumor samples), which is significantly higher than the median TMB of C-RAAS (3.7 mutations per Mb, $n=11$ tumor samples) and primary breast angiosarcoma (1.7 mutations per Mb, $n=18$ tumor samples), ($P=4.49\times10^{-3}$; 95% Confidence Interval (CI), (2.707158, 65.203630) and $P=3.59\times10^{-5}$; 95% CI, (9.701844, 66.368017), respectively). The median TMB of tumors with C-RAAS was significantly higher than that of primary breast angiosarcoma ($P=5.69\times10^{-4}$; 95% CI, (−3.2835076, −0.8439004)). The outline of each violin in the plot shows the mirrored kernel density, with the horizontal line indicating the median. A two-sided Wilcoxon test was used to compare the median TMB for various angiosarcoma subclassifications. **e**, Plot depicting the mutational signature activities across all 47 angiosarcoma tumor samples. The top panel of counts indicates the total number of mutations (*y* axis) attributed to each mutational signature activity within each angiosarcoma tumor sample (*x* axis). The middle panel shows the normalized distribution of signature activities for each sample with the fraction contribution from each of the different signature activities for each sample indicated. The bottom panel shows the associated angiosarcoma subclassification of each sample. Ultraviolet light exposure mutational signature (COSMIC Signature 7, indicated in yellow) is dominant in HNFS tumor samples, which also exhibit high tumor mutation counts. AS, angiosarcoma.

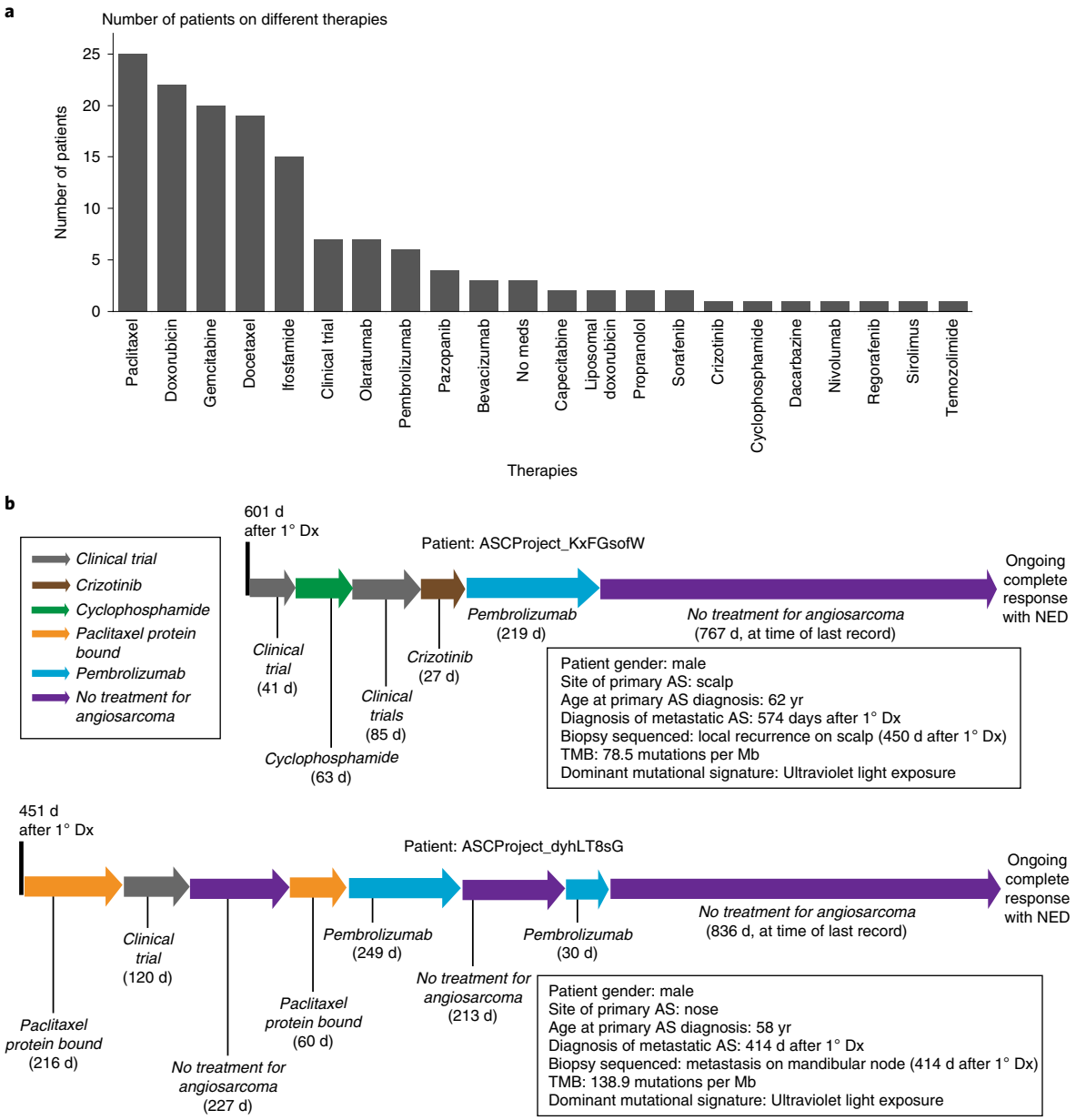

Fig. 4 | Treatments received by the sequenced angiosarcoma patient cohort. a, Bar chart showing the number of patients for whom abstracted medical records indicate that they received the given treatment for angiosarcoma listed on the *x* axis. This graph depicts the treatments taken by 32 patients with angiosarcoma, as well as 3 patients who received no medications ('No meds') according to their medical records. One patient had insufficient medical records from which to abstract treatment data, and is not included in this chart. **b**, Timeline of treatments received by two patients with HNFS angiosarcoma (ASCProject_KxFGsofWAS and ASCProject_dyhLT8sG) in the metastatic setting who each had a complete response to pembrolizumab, as determined by the medical records obtained by study staff. Any time period greater than 200 d in which these patients received no therapy for angiosarcoma is shown. These two patients also exhibited a high TMB and a dominant ultraviolet light exposure mutational signature. 1° Dx, primary diagnosis.

to larger academic medical institutions. The use of online engagement and patient-driven registration may be predicted to skew the demographics of study subjects toward younger or less sick patients; however, we found that the average age at angiosarcoma diagnosis in our cohort was just slightly lower than that of a single institution angiosarcoma study[2] (53 and 62 years, respectively) and that more than a third of patients (86 out of 227) enrolled within one year of their primary angiosarcoma diagnosis.

This research approach allowed us to rapidly provide a detailed clinically annotated genomic landscape of a rare cancer, angiosarcoma, which allowed us to identify important recurrent genomic alterations. Angiosarcomas have been classified traditionally by site of origin or by an environmental or iatrogenic exposure such as prior therapeutic radiation[4–10], whereas the use of WES in this cohort of 47 samples allowed us to observe additional forms of angiosarcoma subset stratification that correlate well on a molecular level. In a malignancy with few effective treatment options, new potential therapeutic strategies were identified for patients with particular angiosarcoma subclassifications, including primary breast and HNFS angiosarcoma, which has allowed the sarcoma community to explore the development of new clinical trials. To ensure that the ASCproject data can be widely used by all researchers, the data have been publicly released on https://www.cbioportal.org at regular intervals on a pre-publication basis, with additional data continuing to be released.

The results of the ASCproject suggest that patient-partnered projects may offer a powerful approach for studying cancers. Indeed, the ASCproject is just one of a growing number of patient-partnered projects in different cancers that are part of the 'Count Me In' initiative. The ability to rapidly acquire and analyze samples from geographically dispersed patients using the powerful patient-driven approach democratizes research, couples genomic and molecular data to real-world patient outcomes, and should be explored in other patient populations that are currently challenging to study through traditional mechanisms.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-019-0749-z.

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Methods

Website. The ASCproject website (https://ascproject.org/) was developed in collaboration with patients. The website enables patients with angiosarcoma across the United States and Canada to learn about the project, register for participation in this research study, sign an electronic informed consent, and provide information about themselves and their disease.

Informed consent. Upon completion of online study registration and an intake survey, patients provided informed consent and completed a medical release form in order to be enrolled in the study (Supplementary Table 8). Informed consent was provided by all patients on a web-based consent form as approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board (DF/HCC Protocol 15-057B).

Patient consent allowed the research study team to acquire copies of medical records for abstraction, to send a kit for saliva sample acquisition, to perform sequencing analysis, and to share de-identified linked, clinical, genomic, and patient-reported data publicly. Patients could also opt in to consent to provide a blood sample and/or allow procurement of archived tumor samples for sequencing of germline and tumor DNA.

The analyses conducted for this study were performed with information and samples from patients who consented between 1 January 2017 and 30 September 2018.

Patient-reported data. The patient-reported data for this study consisted of patient responses to the intake survey that accompanied the initial online project registration (Supplementary Tables 2,8). All 17 questions in this intake survey were optional. Any survey question left blank was categorized as 'Not reported'. Information on format standardization and categorization of patient-reported data is described in the Supplementary Methods.

Acquisition of medical records. For each enrolled patient who completed the medical release form, the study team requested medical records from all institutions and physician offices at which the patient indicated that they received clinical care. Study staff electronically faxed a detailed medical record request form to each facility (Supplementary Table 8). Medical records that had not been received after several months were requested again in the same manner. Medical records were received by fax, mail, or secure electronic message. All medical records were saved to a secure drive.

Acquisition of patient samples. Enrolled patients were mailed separate kits to provide saliva and blood samples (see Supplementary Methods for details). Kits containing samples were mailed back in prepaid envelopes to the Broad Institute Genomics Platform. Samples received at the Broad Institute were logged by their unique barcodes. Saliva samples were stored at room temperature (25 °C) until advancement to WES. Blood samples were fractionated into plasma and buffy coats. Buffy coats were used to extract germline DNA for WES if no saliva sample was available.

If the participant consented to the acquisition of tumor tissue, portions of stored clinical tumor tissue were requested. A form was faxed to each pathology department requesting one H&E-stained slide as well as either 5-µm unstained slides (8–20 slides) or one formalin-fixed paraffin-embedded tissue block. Requests explicitly stated that no sample should be exhausted in order to fulfill the request. Tissue samples were received at the Broad Institute by mail. Tissue samples received as blocks were labeled with unique numerical identifiers and were cut into three 30-µm scrolls per block, which were then labeled with unique barcode identifiers. Tissue samples received as unstained slides were logged and labeled with unique barcode identifiers.

Histological evaluation. One H&E-stained slide and three additional unstained slides of each tumor sample were sent for centralized expert pathology re-review (J.L.H.) to confirm the presence of angiosarcoma in each sample (see Supplementary Methods). Downstream analysis was performed only for samples that were confirmed to be angiosarcoma.

Whole exome sequencing and data analysis. Samples were submitted to the Broad Institute Genomics Platform for processing and sequencing. DNA was extracted from primary and metastatic tumors (for somatic DNA), as well as from saliva or blood plasma samples (for germline DNA), and WES was performed, as detailed in the Supplementary Methods. Sequencing data were processed and analyzed to identify somatic single nucleotide variants, small insertions or deletions and copy number alterations using established cancer genomics pipelines at the Broad Institute (see Supplementary Methods). Recurrently altered genes were determined based on the frequency of somatic alteration in approximately 680 cancer-related genes (https://cancer.sanger.ac.uk/census, https://pathcards.genecards.org). MutSig2CV was used to infer significantly recurrent mutated genes in the cohort[13]. TMB was calculated as the total number of mutations (non-synonymous plus synonymous) detected for a given sample divided by the length of the total genomic target region captured with WES[27]. SignatureAnalyzer was used to identify mutational signatures within the cohort, and these were further validated using deconstructSigs for individual tumor samples (see Supplementary Methods).

***PIK3CA* analysis.** To assess *PIK3CA* dependency, CRISPR gene knockout dependency data (Avana data set), cancer cell line mutation calls, and associated cell line and mutation annotations were taken from the DepMap 19Q1 data release (https://depmap.org/portal/download). CRISPR knockout gene dependency scores for cell lines with wild-type *PIK3CA* were compared to those of cell lines harboring hotspot *PIK3CA* mutations and to those of cell lines with *PIK3CA* mutations observed in this angiosarcoma cohort (see Supplementary Methods). Structural analysis to map *PIK3CA* mutations was performed using PyMOL and the p110alpha protein structure (PDB ID: 3HHM). Public cancer genome data sets were used to investigate *PIK3CA* mutations (see Supplementary Methods).

Statistical analyses. A two-sided Wilcoxon rank sum test was used to calculate significance for comparison of TMB across various angiosarcoma subclassifications. A two-sided Fisher's exact test was used to calculate significance for univariate frequency comparisons. For dependency data analysis of *PIK3CA* mutations, statistical comparisons were performed using a two-sample, two-sided unpaired *t*-test. A P value of <0.05 was considered to be statistically significant. All statistical analysis was performed using R (version 3.5.2).

Medical record abstraction of clinical data. Using a clinical data model that was developed with multiple sarcoma experts, 40 predetermined clinical fields were abstracted from each medical record independently by two trained study staff abstractors (see Supplementary Methods). Quality control for concordance was performed by a third trained abstractor. If required, fields may have received additional review from physicians with expertise in the care of patients with angiosarcoma. Dates were abstracted to the greatest level of detail available in the record, and all dates reported publicly are based on time elapsed relative to the date of primary diagnosis, as described in Supplementary Methods.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

To protect patient confidentiality, the study data set is de-identified before it is shared, which includes the masking of patient IDs and the reclassification of unique patient-reported demographic responses as 'other' (see Supplementary Methods). The resulting clinically annotated genomic data set of the ASCproject is shared publicly on cBioPortal on an ongoing and regular basis as the data are generated; the ASCproject has been registered as a study at dbGaP under the accession number phs001931 (contact data@ascproject.org with any questions regarding data availability).

Code availability

All software and pipelines for genomic data generation are described in detail in Supplementary Methods. Information on the scripts used to generate the figures is accessible upon request from the corresponding author.

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Author contributions

C.A.P., M.D. and R.E.S. oversaw patient enrollment and sample collection; C.A.P., R.E.S. and M.D. assisted with acquisition and annotation of clinical samples; J.L.H. conducted pathology review; C.A.P., B.S.T., A.L.D., S.S., D.K., Y.-L.C., P.M. and B.A.V.T. designed or performed clinical data abstraction and annotation; M.D and R.E.S. assisted with processing patient-reported data; E.J. performed the computational analyses; E.J. and J.G.T.Z. evaluated and analyzed the DepMap data; C.A.P. performed structural modeling; E.J., B.N.T. and R.E.S. led the process of public data release; C.P.R., G.D.D., T.R.G. and E.S.L. provided advice and guidance on the study; C.A.P., E.J., B.N.T. and M.D. generated figures; C.A.P., E.J., B.N.T. and N.W. wrote the manuscript with additional input from all authors; C.A.P. and N.W. supervised the study. All authors reviewed and approved the manuscript.

Competing interests

C.A.P. is a nominal stockholder in Supernus Pharmaceuticals. C.A.P. has received sponsored research support from Eisai Inc. J.L.H. is a consultant to Eli Lilly and Epizyme. G.D.D. reports the following interests: grants, personal fees, non-financial support and travel support to consulting meetings from Novartis, Bayer, Roche, Epizyme and Daiichi-Sankyo; grants, personal fees and travel support to consulting meetings from Pfizer; personal fees and travel support to consulting meetings from EMD-Serono; personal fees from Sanofi; grants and personal fees from Ignyta; grants, personal fees and travel support to consulting meetings from Loxo Oncology; grants, personal fees and non-financial support from AbbVie; personal fees and travel support to consulting meetings from Mirati Therapeutics; personal fees and travel support to consulting meetings from WIRB Copernicus Group; personal fees from ZioPharm; personal fees from Polaris Pharmaceuticals; personal fees and travel support to consulting meetings from M.J. Hennessey/OncLive; grants, personal fees and travel support to consulting meetings from Adaptimmune; grants from GlaxoSmithKline; personal fees, minor equity, and travel support to Board meetings from Blueprint Medicines, where he serves as a member of the Board of Directors; personal fees and minor equity options from Merrimack Pharmaceuticals, where he serves as a member of the Board of Directors; personal fees and minor equity from G1 Therapeutics; personal fees, minor equity options and travel support to consulting meetings from CARIS Life Sciences; minor equity options from Bessor Pharmaceuticals; minor equity options from ERASCA Pharmaceuticals; personal fees and travel support to consulting meetings from CHAMPIONS Oncology; grants and personal fees from Janssen; grants, personal fees, travel support to consulting meetings, and non-financial support from PharmaMar. In addition, G.D.D. has a use patent on imatinib for GIST, licensed to Novartis with royalties paid to the Dana-Farber Cancer Institute. E.S.L. serves on the Board of Directors for Codiak BioSciences and Neon Therapeutics, and serves on the Scientific Advisory Board of F-Prime Capital Partners and Third Rock Ventures; he is also affiliated with several non-profit organizations including serving on the Board of Directors of the Innocence Project, Count Me In, and Biden Cancer Initiative, and the Board of Trustees for the Parker Institute for Cancer Immunotherapy. E.S.L. has served and continues to serve on various federal advisory committees. T.R.G. serves or has recently served as a scientific adviser to Foundation Medicine, Inc. (wholly owned by Roche), GlaxoSmithKline, plc, Sherlock Biosciences, Inc., and FORMA Therapeutics, Inc. N.W. was previously a stockholder and consultant for Foundation Medicine, Inc., has been a consultant/advisor for Novartis and Eli Lilly, and has received sponsored research support from Novartis and Puma Biotechnology. None of the for-profit entities had any role in the conceptualization, design, data collection, analysis, decision to publish, or preparation of the manuscript.

Additional information

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Correspondence and requests for materials should be addressed to N.W.

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Results: Engagement Strategy and Project Design

a

Before

1. When were you first diagnosed with angiosarcoma?
Choose month... Choose year...
2. When you were first diagnosed with angiosarcoma, what was the primary site?
- Head/Neck (not scalp)
- Scalp
- Breast
- Heart
- Liver
- Spleen
- Lung
- Brain
- Lymph Nodes
- Bone/Limb
- Abdominal Area
- Other

3. When you were first diagnosed with angiosarcoma, had it spread beyond the primary site?
- Yes
- No
- I don't know

After

1. When were you first diagnosed with angiosarcoma?
Choose month... Choose year...
2. When you were first diagnosed with angiosarcoma, where in your body was it found (select all that apply)?
- Head/Face/Neck (not scalp)
- Scalp
- Breast
- Heart
- Liver
- Spleen
- Lung
- Brain
- Lymph Nodes
- Bone/Limb
- Abdominal Area
- Other
- I don't know

3. Please select all of the places in your body that you have ever had angiosarcoma (select all that apply).

b

Study Staff posted a message on social media:
"Feedback time! Let me know what you think of the mock ups that the designer just sent me. For purposes of comparison, refer to the MBCproject.org website."
Two home page mockups were attached to the post

The post received 24 comments, excerpts include:

"Am not sure what to suggest instead, but I don't like either of the photographs (runner or rowers) they don't suggest anything about AS to me."

"The MBC page picture is dramatic and grabs your attention, neither of these do that for me."

c

d

Study Staff posted a message on social media:
"By a show of likes, can you let me know if you have angiosarcoma and if you would be interested in contributing your tumor samples (we will get them, you only need to sign a consent form for us to get the samples) to the biggest angiosarcoma study to date"

The post received 90 likes and 110 comments

Extended Data Fig. 1 | GRIPP2 Short Form Results: Engagement Strategy and Project Design. (**a**) Patient intake survey, before (top) and after (bottom) incorporation of patient feedback. (**b**) A summary of a social media post by study staff soliciting feedback on potential home page designs and comments from the community. (**c**) The turtle mascot associated with angiosarcoma which, based on patient feedback, was custom designed by the study and is prominently displayed on ASCproject.org as well as on saliva and blood kits. (**d**) A summary of a social media post by study staff polling angiosarcoma patients for interest in participating in ASCproject.org prior to its development. Ninety patients responded affirmatively within days.

Results: Outreach and Accrual

a

Post by patient in social media:
"Welcome to all the new members. I am sorry that you had to find us and join the club that no-one wants to be a member of. However you will find amazing support and information here and now you are here.

You can help fight this [dreadful] disease by taking part in the research that our very own Corrie Painter has been so instrumental in setting up. Anyone can contribute to the questionnaire, but only folks living in Canada and the USA can donate tissue etc.
https://ascproject.org/home "

b

The Angiosarcoma Project's advocacy partners include:

- Sarcoma Alliance for Research through Collaboration
- Sarcoma Foundation of America
- Sarcoma Alliance
- Angiosarcoma Awareness
- TargetCancer Foundation
- The Paula Takacs Foundation for Sarcoma Research

c

Post by advocacy partner in social media:
"CALLING ALL #SARCOMA ORGS: Alert ur constituents to the groundbreaking #Angiosarcoma Project & help researcher study this #cancer! ascproject.org/home @ASCaProject @broadinstitute @corrie_painter @CureSarcoma @SarcomaAlliance @SARCtrials"

d

Post by patient in social media:
"My profile was recently shared on the Angiosarcoma Project Working Group page. I thought I might share it here because I want to remind everyone that if you want to be a part of making progress against Angiosarcoma you can join Count Me In reserach at: https://ascproject.org/home. I was lucky to find this project early in my journey. It helped to give me purpose and more importantly hope. So, if you have AS or are a family member to someone who does, please consider joining the project. Once you sign-up you receive a kit and all you have to do is spit into the tube and send it back. "

e

Post by advocacy partner in social media:
"We are happy to be a supporter of this innovative project and hope its success will lead to better treatments for Angiosarcoma patients.

Angiosarcoma Project:
'Help transform our understanding of Angiosarcoma.
If you have been diagnosed with angiosarcoma, join a nationwide movement of patients, doctors, and scientists by sharing your tumor samples, your medical information, and your voice. Together, we can develop a comprehensive resource that will drive discoveries about this orphan cancer.'
https://ascproject.org/home"

f

Post by advocacy partner in social media:
"True #ASCO17 highlight - seeing rare cancer research innovation in action as our good friends Corrie Painter and Mike Dunphy presented their poster on the Angiosarcoma Project. We are proud to be an advocacy partner on this amazing direct-to-patient research project.
Learn more here: https://ascproject.org"

Extended Data Fig. 2 | GRIPP2 Short Form Results: Outreach and Accrual. (**a**) A summary of a social media post by a patient raising awareness for ASCproject.org and encouraging new patients to visit the project website. (**b**) A list of advocacy partners supporting ASCproject.org. (**c**) A summary of a social media post by an advocacy partner raising awareness for the project through their existing network. (**d**) A summary of a social media post by a patient sharing the value that participation in research holds for them personally, and encouraging others to learn more about the ASCproject. (**e**) A summary of a social media post by an advocacy partner supporting ASCproject.org. (**f**) A summary of a social media post by an advocacy partner promoting a scientific poster presentation and raising awareness for ASCproject.org.

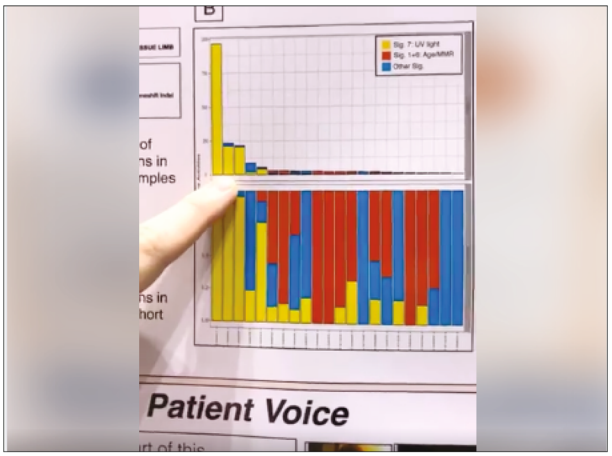
Results: Continued Engagement and Project Iteration

a

Study staff posted a message on social media:
"Good morning! We have updated our map of the USA and Canada, we now have 110 people who have done the initial sign up, 105 have submitted the first survey, 91 have provided consent and 90 have filled out information for the medical release. On this map, you'll see people from 30 states and 2 Canadian provinces."

b

Study staff posted a video of a scientific poster walkthrough on social media:



The video was viewed over 2,100 times. Comments included:

"Really important research on a very nasty cancer. Glad people are into this by sharing info"

"Fantastic work!!!"

"Joining the ASCPROJECT.Org is how this sarcoma gets noticed."

"Great video! Informative and as you say helps shape understand directs further research."

c

Study staff posted a message on social media:
"Awareness time! My colleague, Nikhil Wagle, and I were just invited to DC to present about ASCproject.org (and the MBCproject.org; our sister project) to the NIH (National Institute of Health) in July.

They are keenly interest in the notion of patient-research partnerships and are looking at the early success of our group effort (200 people with an exceedingly rare cancer signed up in under 3 months???!!!) as something that other scientists should adopt to accelerate translational research. This is made possible by all of you, thank you!"

The post received 16 comments, excerpts include:

"Video recording please! This is powerful stuff"

"It would mean a lot for all of us out here to see this achievement"

"I will see what we can do, but in the meanwhile, I will do a video walkthrough for you all of the poster I'm putting together now for a conference that has 40k oncologists that attend!"

"Very cool!!! Thanks"

"Corrie Painter You have really inspired [patient name's] family to spread not just awareness but to think outside of boxes for answers. We want every dr in Canada to know your name."

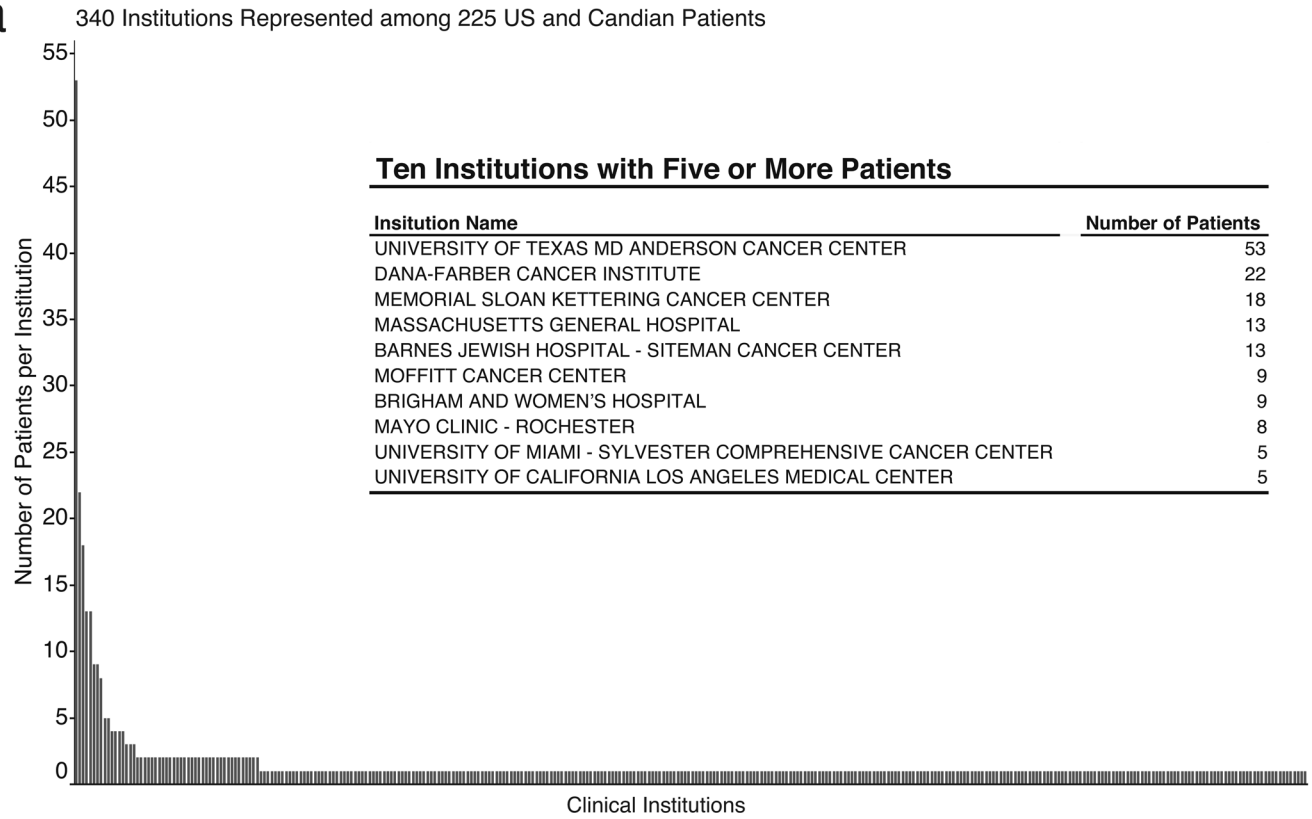
d

Study staff posted a message on social media:
"Data snapshot:
One of our patients asked me about some of the statistics we have for radiation induced angiosarcoma af the breast. As a proxy, I just analyzed data from all people who had previous breast cancer (we will cross reference previous radiation as well in the future).

Of 82 women who reported having a diagnosis of breast angiosarcoma, 40 had previous breast cancer. Of those 40, 27 reported that they were NED at the time of signing up of for the project. The average time since their diagnosis is 4.6 years"

Extended Data Fig. 3 | GRIPP2 Short Form Results: Continued Engagement and Project Iteration. (**a**) A summary of one of 110 social media posts by study staff providing study progress updates. A map was shared representing the first 110 patients to join the study as well as people who completed a survey about a loved one who passed away from angiosarcoma. (**b**) A summary of a live-stream social media post by study staff conducting a lay-friendly video walkthrough of a poster presented at a scientific conference, and comments from angiosarcoma community members. The copyright of the image is owned by a member of the study staff and is shared here with permission. (**c**) A summary of a social media post by study staff sharing an update on an upcoming opportunity to present about the ASCproject at an NIH meeting, and comments from angiosarcoma community members. (**d**) A summary of a social media post by study staff sharing the aggregate results of patient-reported information provided by patients diagnosed with radiation-induced angiosarcoma of the breast in response to questions about the sub-group from the community.

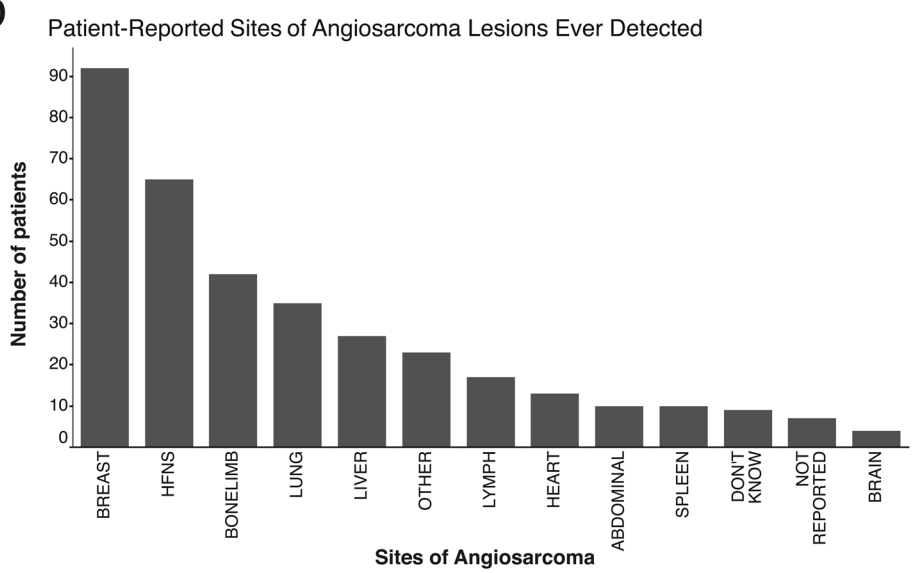
a



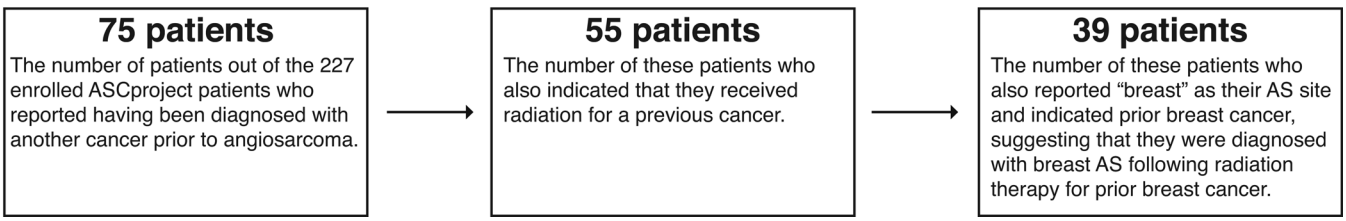
Ten Institutions with Five or More Patients

Insitution Name	Number of Patients
UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER	53
DANA-FARBER CANCER INSTITUTE	22
MEMORIAL SLOAN KETTERING CANCER CENTER	18
MASSACHUSETTS GENERAL HOSPITAL	13
BARNES JEWISH HOSPITAL - SITEMAN CANCER CENTER	13
MOFFITT CANCER CENTER	9
BRIGHAM AND WOMEN'S HOSPITAL	9
MAYO CLINIC - ROCHESTER	8
UNIVERSITY OF MIAMI - SYLVESTER COMPREHENSIVE CANCER CENTER	5
UNIVERSITY OF CALIFORNIA LOS ANGELES MEDICAL CENTER	5

b

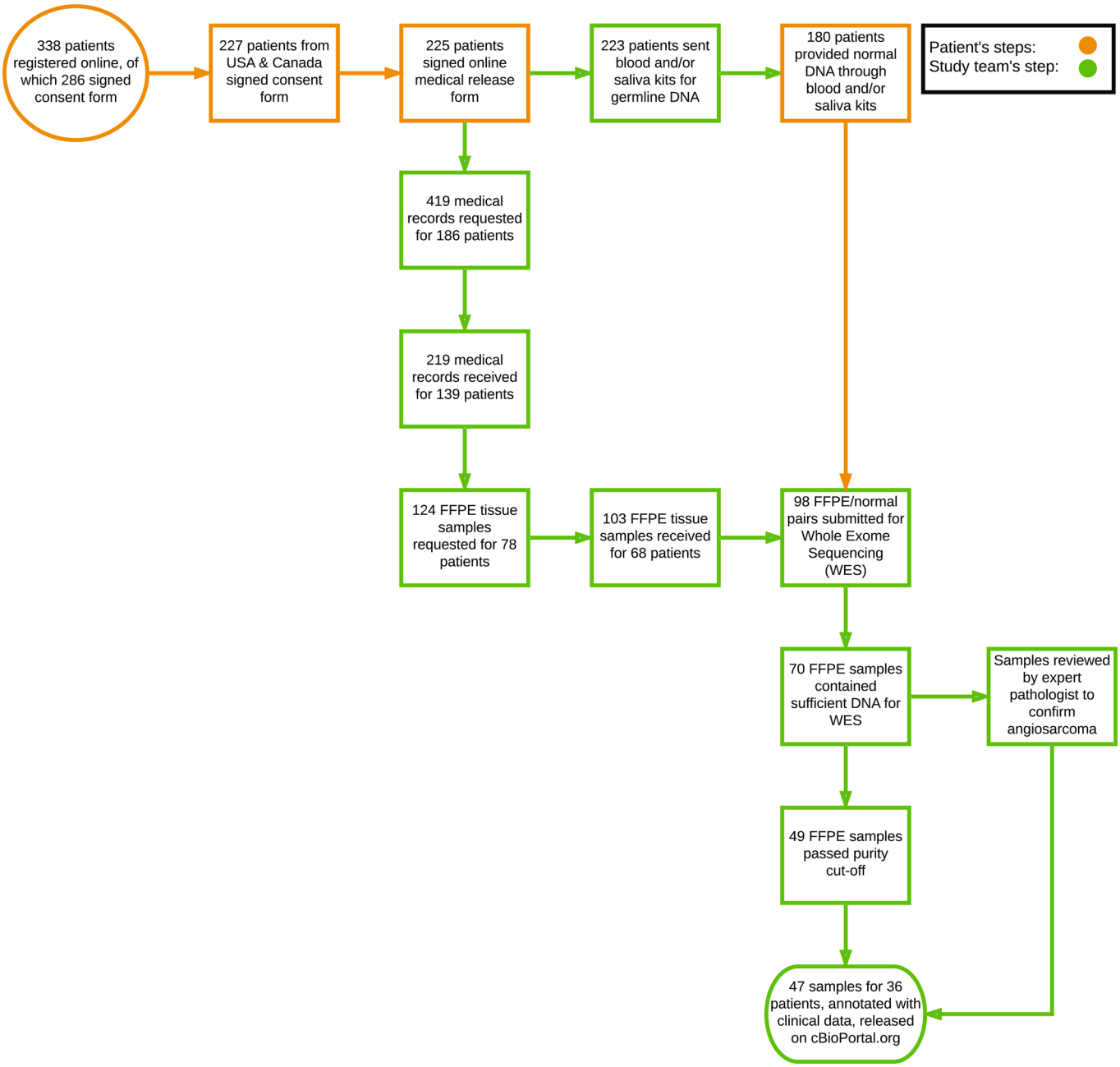


c

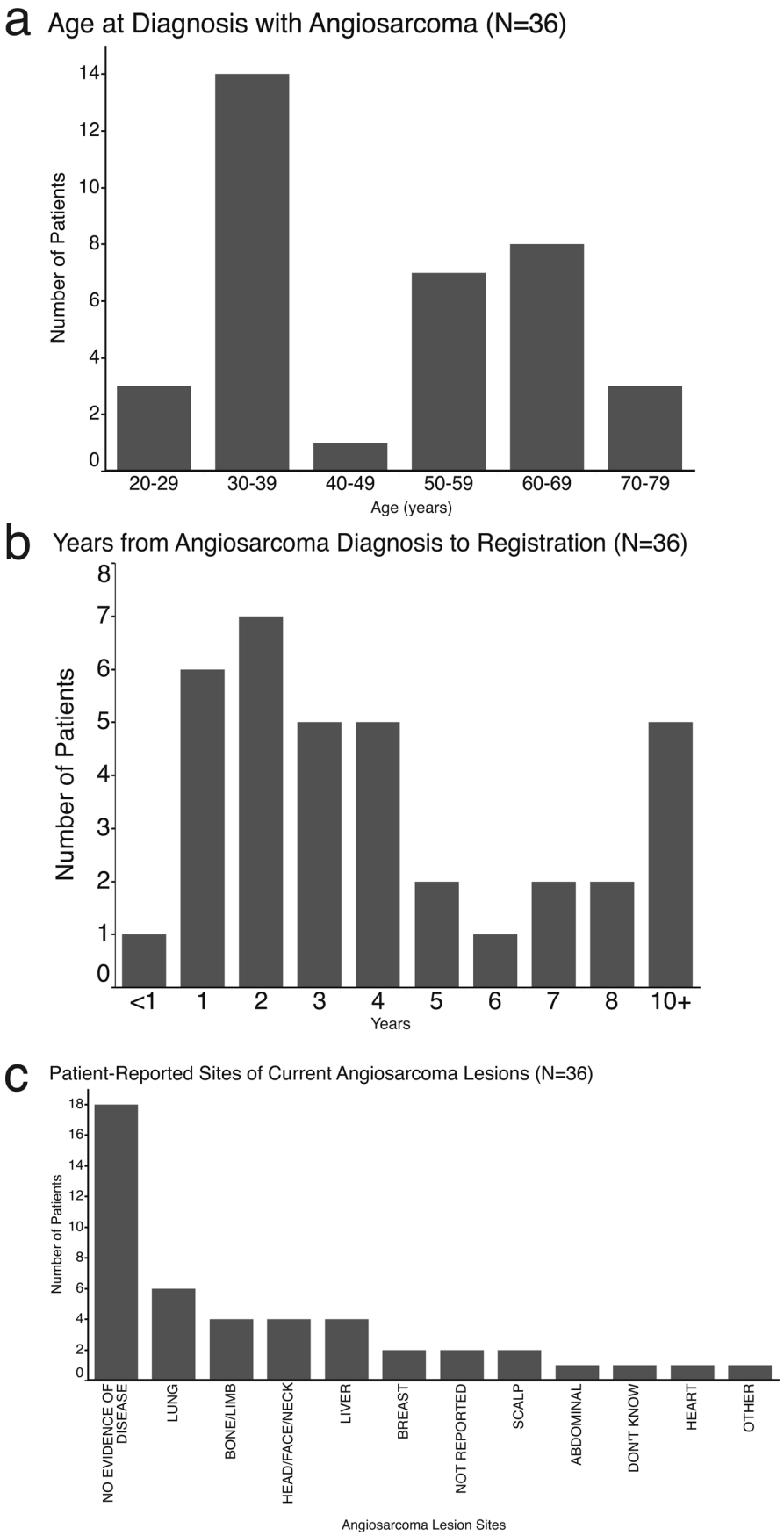


Extended Data Fig. 4 | See next page for caption.

Extended Data Fig. 4 | Additional patient-reported data from the 227 consented AS patients in the Angiosarcoma Project. (**a**) This chart depicts the 340 different clinical institutions that ASCproject patients reported they received some aspect of their clinical care for AS (x-axis) and the number of patients that reported care at any given institution (y-axis). This information was provided on the medical release forms completed by consented Angiosarcoma Project patients (n = 225 patients). Of the 227 consented ASCproject participants, 2 people did not fill out the medical release form, and are not included in this figure. The majority of the 340 total institutions were listed by only one patient. Ten institutions were listed by five or more AS patients as sites of care (box, upper right). (**b**) A bar chart showing the patient responses to the intake survey question 'Please select all of the places in your body that you have ever had angiosarcoma (Please select all that apply).' Patient intake surveys completed by the 227 patients who consented for the Angiosarcoma Project as of September 30, 2018 were analyzed. Each response of a location is counted separately, such that multiple locations are shown for patients that selected more than one answer to indicate that they have had more than one location for their angiosarcoma lesions. 9 patients selected the provided response option of 'I don't know' ('Don't Know'), and 7 patients did not respond to this question ('Not Reported'). The HNFS category depicted above includes patient responses of 'head, face, neck' and responses of 'scalp.' (**c**) Patient-reported information regarding other cancer diagnoses prior to angiosarcoma. Patient intake surveys completed by the 227 patients who consented for the Angiosarcoma Project as of September 30, 2018 were analyzed to obtain patient-reported information regarding other cancer diagnoses prior to angiosarcoma. Seventy five patients' responses indicated they had been diagnosed with another cancer prior to angiosarcoma. These patients were identified based on their responses of "Yes" to the survey question "Were you ever diagnosed with any other kind of cancer(s)?". Patients also provided specific diagnoses years for AS and other cancer(s), which were used to determine that the AS diagnosis occurred in the same year or after another cancer diagnosis. Of those 75 patients, 55 also responded "Yes" to the survey question "Have you had radiation as a treatment for another cancer(s)?". Of those 55 patients, 39 also reported "breast" as their only primary AS site and indicated breast cancer as a previous cancer. The majority of these 39 patients are expected to be cases of cutaneous AS of the breast. AS, angiosarcoma; ASCproject, The Angiosarcoma Project; HNFS, head, neck, face, scalp.

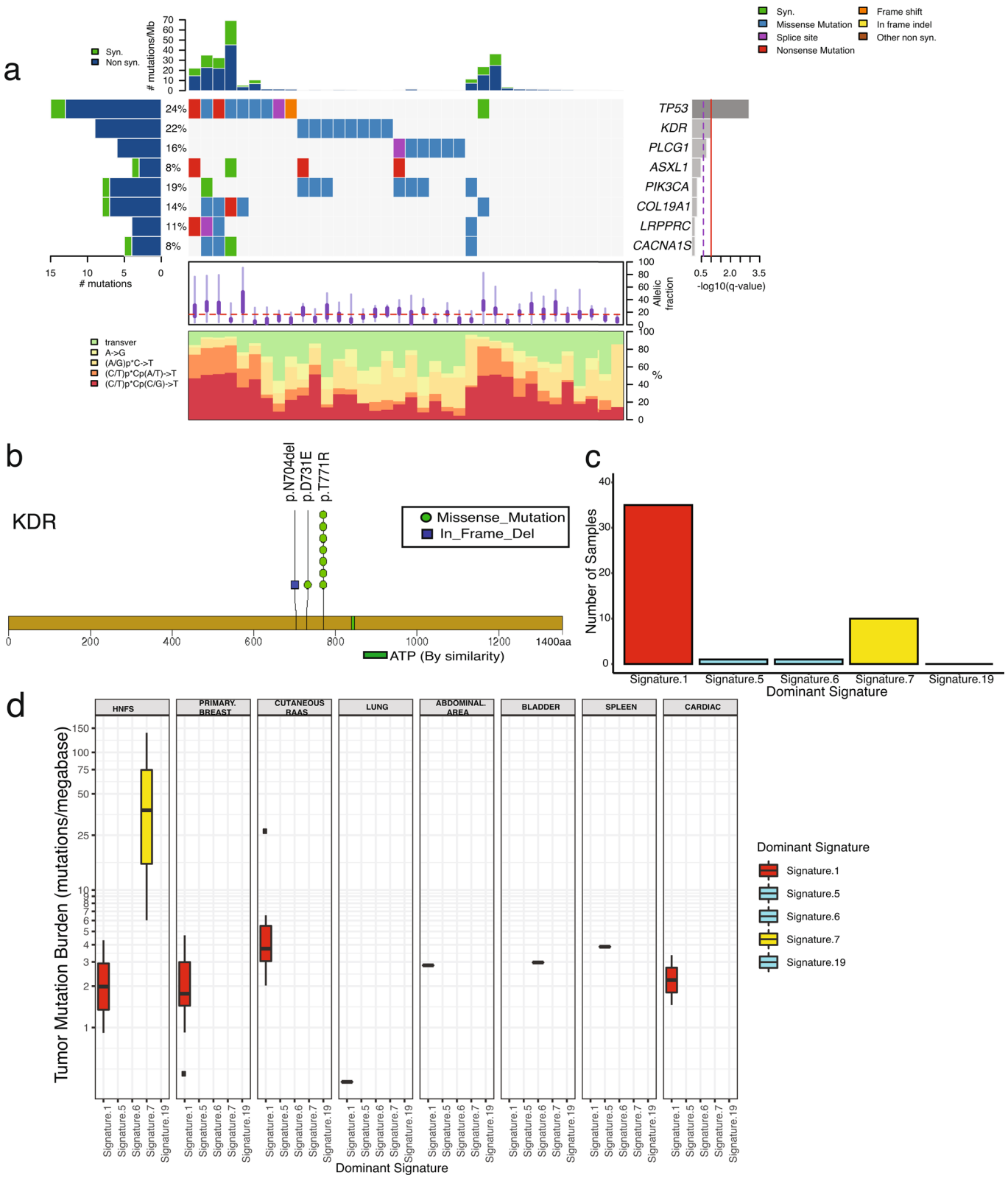


Extended Data Fig. 5 | Detailed diagram of each step of the Angiosarcoma Project. This diagram shows additional information regarding the attrition at various steps in the Angiosarcoma Project. Numbers indicated are as of September 30, 2018. 59 patients who signed the consent form did not provide a country of residence or indicated they were living outside of the U.S. or Canada. 2 patients did not sign the release form. 2 patients were not sent blood or saliva kits, including one patient who passed away before kits could be sent and another who provided an invalid mailing address. 43 patients did not return either their blood or saliva kits. 39 of 225 patients who signed the medical release form were in the study staff's medical record request queue as of September 30, 2018. 200 of 419 requested medical records were not received (55 requests resulted in denials by medical record departments, and 145 requests did not get a response). 61 patients' records either did not contain sufficient information to request tissue or showed too little tissue to request for research. 21 requested FFPE samples have not yet been received. 5 received FFPE samples did not have available matched normal DNA (from blood or saliva) and were not initiated for sequencing. 28 submitted paired samples have not been sequenced (16 samples had insufficient material for sequencing and 12 sets of samples are still in the sequencing pipeline). 21 sequenced samples had less than 10% tumor purity. 2 samples were excluded from the dataset because centralized pathology review determined the samples were not angiosarcoma. The remaining 47 FFPE samples from 36 patients that underwent whole exome sequencing comprised the Angiosarcoma Project September 2018 dataset that was released on cBioPortal.org along with associated patient-reported and clinical data.



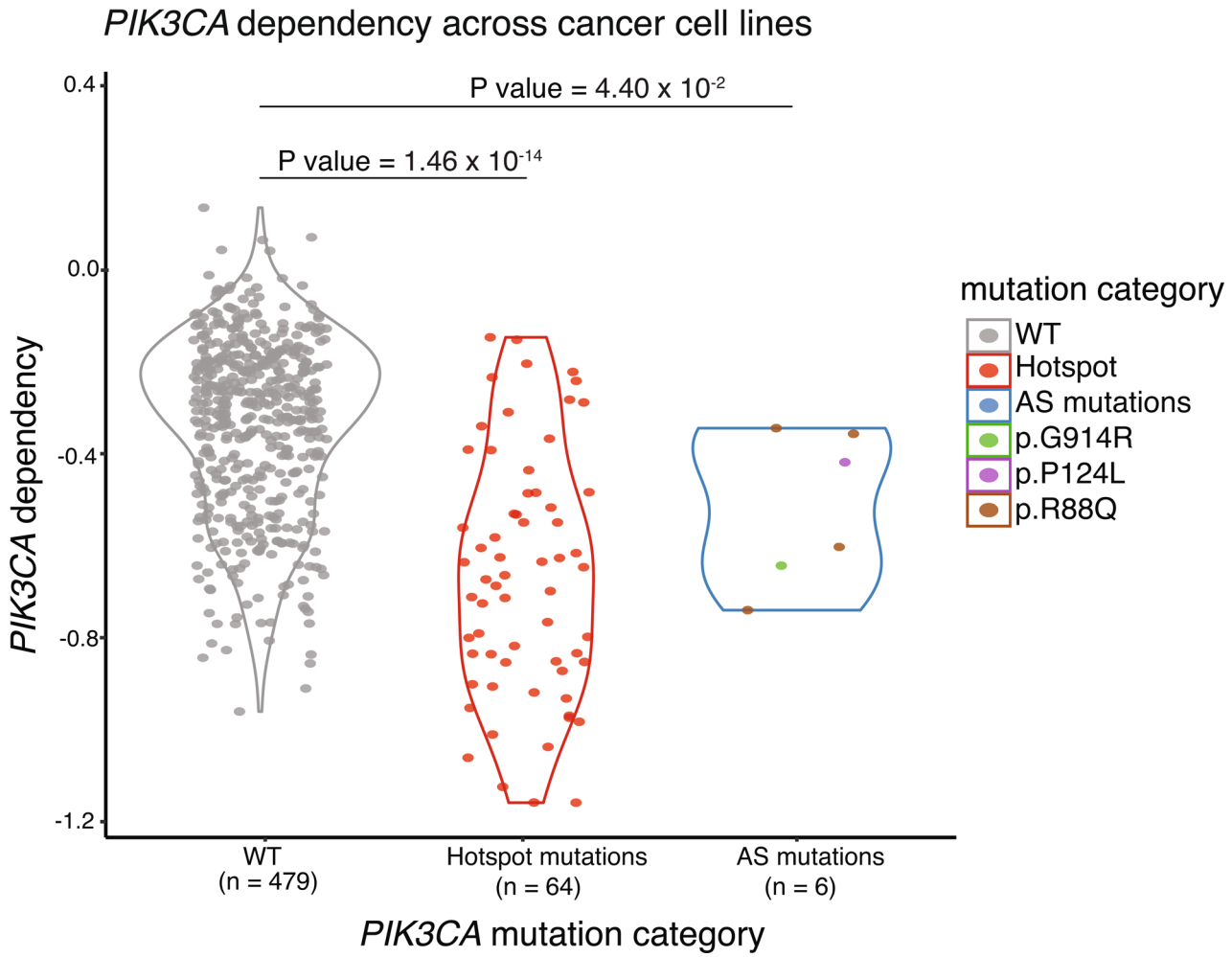
Extended Data Fig. 6 | See next page for caption.

Extended Data Fig. 6 | Patient-reported data from the 36 AS patients whose samples were sequenced in the Angiosarcoma Project. The intake survey completed during the ASCproject registration process by these 36 patients were analyzed. (**a**) A bar chart showing the age in years of these 36 patients at initial diagnosis with AS (mean: 47.8 years). These values were calculated from patient provided date of birth and date of initial AS diagnosis. (**b**) A bar chart showing the years elapsed between these 36 patients' initial diagnosis with AS and patients' registration in the ASCproject (mean: 4.6 years). These values were calculated from the date of project registration and the patient-provided date of initial AS diagnosis. (**c**) A bar chart showing the patient-reported location of angiosarcoma at the time of last intake survey completion. An option was provided for patients to report no evidence of disease. Patients with more than one location of AS were able to provide more than one site. 2 patients did not respond to this question ('Not Reported') and 1 patient responded 'Don't Know.' AS, Angiosarcoma; ASCproject, The Angiosarcoma Project.

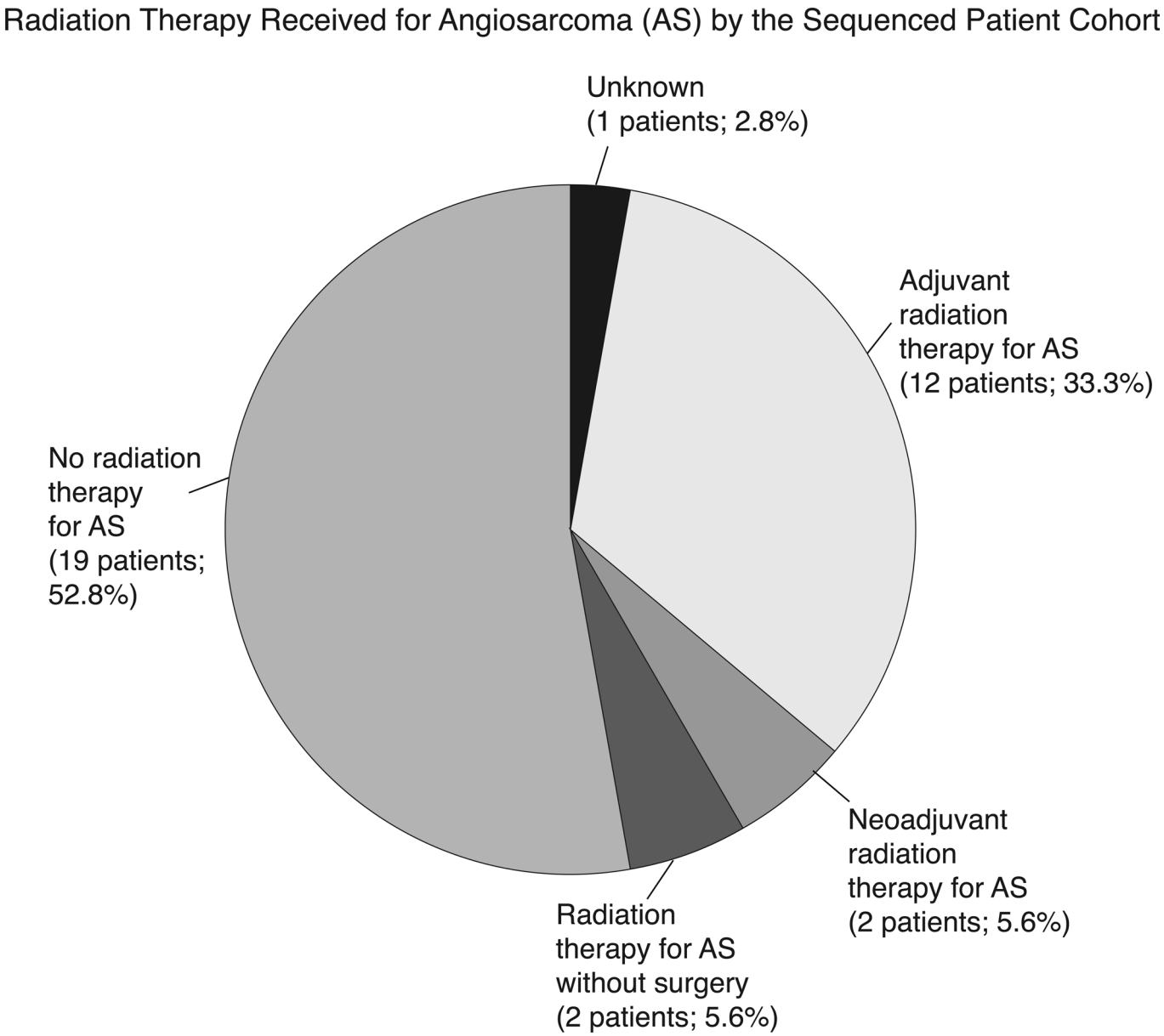


Extended Data Fig. 7 | See next page for caption.

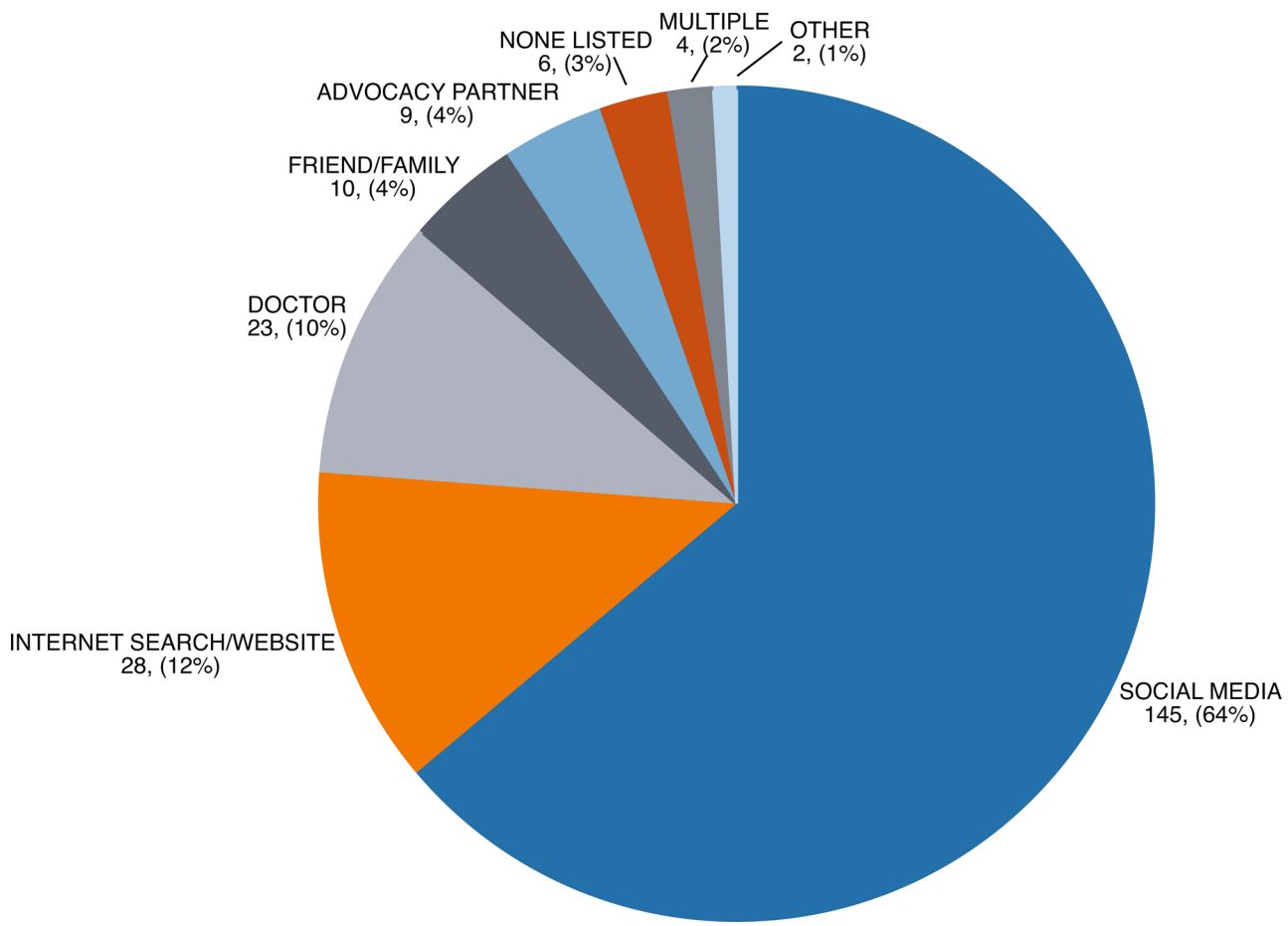
Extended Data Fig. 7 | Recurring alterations and dominant mutational signatures in angiosarcoma. (**a**) Co-mutation plot shows significantly recurring mutated genes among (N=36 patients) AS patients. *TP53* and *KDR* are significantly mutated across the cohort. The p-values were computed using fisher's method and truncated product method. FDR (q values) were generated using Benjamini and Hochber method to correct for multiple hypotheses. Genes that have the –log 10 q value >=1 (red line) are significant. Box plot of the allelic fractions of the mutations in individual tumors is shown below the mutation plot. The horizontal red line represents median and the whiskers to extend to the data extremes. (**b**) Stick plot of *KDR* showing the recurrent mutations and their positions that were identified in this AS cohort. (**c**) Bar graph representing the number of tumor samples (y-axis) that are grouped based on 5 dominant mutational signature categories (x-axis). (**d**) Box plot representing the distribution of TMB (y-axis) for N=47 tumor samples across five mutational signature processes (as defined by COSMIC) identified in this cohort and categorized among 8 AS subclassifications (x-axis). Samples with dominant signature 7 (yellow, N=10 tumor samples) which corresponds to UV light exposure, have the highest median TMB and this signature was only observed in HNFS AS. Horizontal bars indicate median values, while the boxes show the IQR. The whiskers extend to 1.5× the IQR on either side. AS, Angiosarcoma; TMB, tumor mutation burden, HNFS; head, neck, face, scalp.



Extended Data Fig. 8 | *PIK3CA* mutations found in primary breast angiosarcoma are likely activating. Sensitivity to CRISPR knockout-induced loss of *PIK3CA* (*PIK3CA* dependency) was calculated for three groups of cancer cell lines using the Dependency Map dataset (depmap.org): lines containing (1) wild-type *PIK3CA* (gray), (2) *PIK3CA* hotspot mutations (red), and (3) *PIK3CA* mutations seen in AS patients (R88Q [4 lines], P124L [1 line], G914R [1 line]; (colored)). *PIK3CA* hotspot mutations were defined (depmap.org) using their frequency of occurrence in TCGA and COSMIC databases. Relative to cell lines with wild-type *PIK3CA*, *PIK3CA*-mutant cell lines are significantly more sensitive to CRISPR knockout-induced loss of *PIK3CA* (*PIK3CA* hotspot mutant (n=64 cell lines, median=-0.669, minimum=-1.16, maximum=-0.147) vs *PIK3CA* WT (n=479 cell lines, median=-0.298, minimum=-0.961, maximum=0.135), p-value = 1.46 x 10-14, mean difference = -0.328, 95% CI: (-0.396,-0.260)); cell lines with *PIK3CA* with AS mutations (n=6 cell lines, median=-0.511, minimum=-0.740, maximum=-0.344) vs *PIK3CA* WT (n=479 cell lines, median=-0.298, minimum=-0.961, maximum=0.135), (p-value = 4.40 x 10-2, mean difference = -0.181, 95% CI: (-0.355,-0.007)). Statistical comparisons were performed using a two-sample, two-sided unpaired t-test. WT, wild-type; AS, angiosarcoma.



Extended Data Fig. 9 | Radiation therapy received for angiosarcoma by the sequenced patient cohort. A pie chart showing information regarding radiation treatments received by the 36 sequenced patients in the cohort. This information was abstracted from obtained medical records. These radiation therapies may have been given in conjunction with pharmacological and/or surgical interventions. Patients were categorized into groups depicted in pie chart: patients who received neoadjuvant radiation (2 patients), patients who received adjuvant radiation (12 patients), patients who received radiation for AS without surgery (2), and patients who did not receive radiation for AS (19). For one patient who was categorized as 'Unknown', the medical records were not sufficient to abstract this information. AS, angiosarcoma.



Extended Data Fig. 10 | Patient referral source to the Angiosarcoma Project. A pie chart showing patient responses to the patient intake survey question 'How did you hear about The Angiosarcoma Project?.' Patient intake surveys completed by the 227 patients who consented for the Angiosarcoma Project as of September 30, 2018 were analyzed. Each free text patient response was grouped into the categories depicted in pie chart. Unique responses from 2 patients were grouped together as 'Other.' 4 patients reported more than one referral source ('Multiple'). 6 patients did not respond to the question ('None Listed').

nature research

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Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

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☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection

All software and methods for genomic data generation is described in detail in Supplementary Methods.
All genomics data collection software and tools used in this study are published and/or publicly available. Exome BAM files were produced with the Picard pipeline (http://picard.sourceforge.net).

Data analysis

All software and pipelines for genomic analysis are described in detail in Supplementary Methods.

All genomics analysis software and tools used in this study are published and publicly available. Whole exome genomic analysis was performed with the Firehose environment (http://www.broadinstitute.org/cancer/cga/Firehose) using genomics tools available at http://www.broadinstitute.org/cancer/cga. As detailed in the Supplementary Methods section, these tools include: ConTest, MuTect, Indelocator, SvABA, Recapseg, GISTIC, Strelka, Mutect2, Novoalign, Oncotator, GATK Haplotype Caller, MutSig2CV and Absolute.

--Mutational Signature analysis was performed using the following publicly available tools as described in the Supplementary Methods:
1. Signature Analyzer (https://software.broadinstitute.org/cancer/cga/msp)
2. DeconstructSig (https://github.com/raerose01/deconstructSigs)
--Protein structure visualization analysis was performed using PyMOL (The PyMOL Molecular Graphics System,325 Version 1.2r3pre, Schrödinger, LLC.)
--As described in the Supplementary Methods, the following additional publicly available datasets were used for analysis and validation:
1. Cancer Dependency Map - DepMap 19Q1 data release (https://depmap.org/portal/download/)
2. AACR-GENIE - GENIE version 5 (http://genie.cbioportal.org/)

Additionally, the following software/tools were used to analyze data:
1. Picard (http://picard.sourceforge.net) – version 2.10.10
2. ConTest - GenomeAnalysisTK-3.1
3. BWA Aligner -version 0.5.9
4. Mutect version 1.1.6-0-g6fe4f4c

5. Mutect2 Version=3.4-45-g6e00632
6. GATK Haplotype Caller Version=3.1-1-g07a4bf8
7. NovoAlign - version .novocraft-2.07.18
8. Strelka version 2.0.13
9. SvABA version 0.2.1
10. Indelocator – GenomeAnalysisTK-3.1
11. Oncotator v1.9.1.0
12. MutSig2CV – v3.1
13. ReCapseg (BEAGLE, HAPMAP)- 1.5.0.0
14. GISTIC version 2.0.22
15. Absolute version 1.06
16. Signature Analyzer version 1
17. DeconstructSig version 1.8.0
18. PyMOL Version 1.2r3pre
19. R 3.5.2
20. Tableau 2018.3

A two-sided Wilcoxon's rank sum test was used to calculate significance for comparison of TMB across various AS subclassifications. A two-sided Fisher's exact test was used to calculate significance for univariate frequency comparisons. For dependency data analysis of PIK3CA mutations, statistical comparisons were performed using a two-sample, two-sided unpaired t-test. A p-value of < 0.05 was considered to be statistically significant. All statistical analysis was performed using R (version 3.5.2).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

De-identified patient-reported and clinical data, as well as analyzed genomic data generated by the Angiosarcoma Project is currently available at cBioPortal for Cancer Genomics (cBioPortal.org; https://www.cbioportal.org/study/summary?id=angs_project_painter_2018). The study dataset is de-identified and patient ID's are masked before it is shared in order to protect patient confidentiality (see Supplementary Methods for more details). There are no restrictions on data availability. Please include a citation statement to accompany any publication that uses the Angiosarcoma Project dataset: "The results included here include the use of data from The Angiosarcoma Project (https://ascproject.org/), a project of Count Me In (https://joincountmein.org/)."
The ASCproject has been registered as a study at dbGaP under the accession number phs001931.
Contact data@ascproject.org for additional details regarding data generated by the Angiosarcoma Project.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size for this study could not be pre-determined given that this project works with a rare cancer population and implemented a new patient-partnered research approach. As such, assumptions about sample size were not possible. To the best of our knowledge, this is the largest reported cohort of angiosarcoma samples that have undergone whole exome sequencing. The Angiosarcoma Project is an ongoing sequencing study of angiosarcoma. As of September 30, 2018, 227 angiosarcoma patients consented to enroll in the study. We performed whole exome sequencing on the 70 tumor samples paired with a matched normal sample (saliva or blood) that had been obtained by this time. Forty-seven samples from 36 patients were used for subsequent genomic analysis after assessment of sufficient tumor purity (greater than or equal to 10%) and confirmation as angiosarcoma by centralized pathology review (Extended Data Figure 5 details attrition). Apart from these considerations, there were no additional selection criteria for these 47 samples.
Data exclusions	As described above in the 'Sample size' section above, some tumor samples that underwent whole exome sequencing were subsequently excluded from subsequent genomic analysis due to quality-control. For inclusion in subsequent genomic analysis, samples needed to contain at least 10% tumor purity (as estimated by Absolute) and also had to be confirmed as angiosarcoma (through centralized pathology review). This sequencing QC and pathology review criteria were pre-established. Extended Data Figure 5 includes additional details regarding sample attrition.
Replication	No replication was performed in this study.

Randomization	No randomization was used in this study as it is an observational study.
Blinding	No blinding was used in this observational study as all patients by entry criteria had a diagnosis of angiosarcoma.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	This study did not involve a clinical trial and no intervention was performed as part of this research. Patients' medical records and biological samples (tumor, saliva, and/or blood) were obtained with their informed consent and the approval of the institutional review board, as described in Methods and Supplementary Methods. Through an online web-portal (https://ascproject.org/), this study was open for enrollment to all patients with angiosarcoma living within the United States and Canada. Information regarding enrolled patient demographics, disease characteristics, and clinical treatments is described in the manuscript and and shown in Figures (e.g. Figures 1B,2A-C, 3A, 4A and Extended Data Figures 4, 6, 9) and Supplementary Tables 2, 3, 6, 7. Patient demographics for the overall cohort of 227 consented patients and the 36 patient subset whose samples underwent sequencing include: age at diagnosis with angiosarcoma (mean: 53.1 years) and years from angiosarcoma diagnosis to ASCproject registration (mean: 3.6 years). Additionally, clinical disease characteristics such as sites of current lesions and sites of lesions ever detected are presented.
Recruitment	This project does not directly recruit patients through any recruitment offices or specific clinical institutions. Enrollment for this project is patient-driven and achieved through a web-based portal (https://ascproject.org/). This study is open for any patients with angiosarcoma who live within the United States and Canada. Patients learn about this project from other patients, through word-of-mouth, and via social media, as well as from scientific outreach and presentations. Enrolled patient-reported referral sources to the Angiosarcoma Project are depicted in Extended Data Figure 10. Due to the web-based enrollment of the Angiosarcoma Project, there is a selection for patients with access to the Internet. The language used in the enrollment and consent process is English, which will select for patients comfortable with this language. Although this use of online engagement and patient-driven registration may be predicted to skew the demographics of study subjects toward younger or less sick patients, we found that the average age at AS diagnosis in our cohort was just slightly lower than that of a single institution AS study2 (53 and 62 years, respectively) and that more than a third of patients (86/227) enrolled within one year of their primary AS diagnosis.
Ethics oversight	The study protocol was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board (DF/HCC Protocol 15-057B).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	This study did not involve a clinical trial.
Study protocol	The study protocol is DF/HCC Protocol 15-057B, as approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board. Additional information regarding study procedures and protocols can be found in Methods and Supplementary Methods of this manuscript.
Data collection	The Angiosarcoma Project is ongoing and was launched in January 2017. This study has web-based project enrollment, consent, and a patient intake survey. This publication analyzes information and samples associated with patients who registered for the Angiosarcoma Project between January 1, 2017 and September 30, 2018. Medical record and tissue sample acquisition: Study staff called the offices of the hospitals and physicians listed in each participant's medical release form to confirm the fax

number for the medical records department. A detailed request was electronically faxed to each facility that asked for medical records (MR) including clinic notes from treating providers, angiosarcoma treatment data (including radiation and chemotherapy), pathology reports, operative reports, referrals, MD to MD exchange, and genetic testing reports from the date of primary diagnosis through to the date of the request (see Supplemental Table 8 for request form). MR that had not been received after several months were re-requested in the same manner. MR were received by fax, mail, or secure electronic message. All MR were saved to a secure drive to facilitate abstraction.

Medical Record Abstraction:
For each consented patient, medical records were requested from all doctors and institutions based in the U.S. and Canada that were listed by the patient in their medical release form. If records were received electronically, they were stored in a secure drive by study staff. Records received in a hard-copy paper format were scanned and securely stored in the same secure drive. To help facilitate manual abstraction, scanned medical records were converted to searchable PDF files by using the Optical Character Recognition (OCR) engine known as Tesseract (LSTM model inside Tesseract version 4.0; (https://github.com/tesseract-ocr/tesseract)). Using the medical records received, 40 pre-determined clinical fields were manually abstracted for each patient. These clinical fields are listed in detail in a clinical data model that was developed with multiple sarcoma experts (data dictionary available upon request).

To ensure data integrity, these 40 fields from each medical record were independently abstracted by two different trained abstractors on the study staff. Quality control (QC) for concordance among abstracted data elements was performed by a third trained abstractor. During the QC process, the third abstractor compared all abstracted fields from the other two abstractors. For any clinical fields that lacked 100% concordance, the QC abstractor went back to the records to review. If the QC abstractor was unable to reconcile differences, these fields received additional review from physicians that are experts in angiosarcoma.

When noted in the medical records, dates of diagnoses and treatments were abstracted to the greatest level of detail available in the record. Dates reported in the medical record only as a year were abstracted as the first of the year. Dates reported in the medical record only as a month and year were abstracted as the first of the month. Dates that could be inferred based on notes were indicated as estimated and not directly abstracted. In order to protect patient confidentiality, all dates reported were based on elapsed time relative to the date of primary diagnosis.

Outcomes

Outcome measures were not considered in this study.