**SUPPLEMENTARY LEGEND AND FIGURES**

**Supplementary Figure 1. Radiotherapy-induced sarcomas in pediatric cancer survivors**

A. Radiation dosimetry shows the radiation dose levels delivered to Patient 1’s initial malignancy, a pelvic rhabdomyosarcoma. Individual radiation isodose lines (shown in the key) are displayed on serial axial CT images (left and right) to indicate the radiation dose levels to which target and normal tissues were exposed. B. Axial MR images (left and right) of Patient 1 demonstrate a new heterogeneously enhancing mass in the previously irradiated volume. This lesion was biopsied and found to be consistent with high grade (3/3) chondroblastic osteosarcoma. C. H&E-stained sections of Patient A’s tumor, a highly pleomorphic sarcoma, are shown at 100X (left) and 400X (right) magnification.  The immunophenotyping (not shown) was negative for markers for either smooth or skeletal muscle. The numerous atypical, nonsymmetric mitoses suggest that it is likely to be highly aneuploid with large scale chromosomal losses and gains. D. Radiation isodose lines from Patient 2’s initial radiotherapy are shown on axial (right) and coronal (left) images from the radiotherapy planning CT scan. Radiation isodose lines indicate the radiation dose levels to which target and normal tissues were exposed. E. MRI of the Patient 2’s pelvis demonstrates no evidence of the original tumor, however a new enhancing lesion has arisen in the right lateral thigh (axial image on right, coronal image on left). The corresponding coronal MR image is shown on the left. F. H&E-stained sections of Patient B’s tumor, a chondroblastic subtype osteosarcoma. Malignant tumor cells produce cartilage and osteoid and are shown at 100X (left) and 400X (right).

**Supplementary Figure 2. Exome coverage achieved with WES**

**Supplementary Figure 3. Somatic variants in radiation-induced SMNs**

A. Frequencies of specific types of base substitutions in SNVs (synonymous and non-synonymous SNVs) pooled from all samples. B. Frequencies of indels, synonymous SNVs, non-synonymous SNVs and SNVs in non-coding regions shown.

**Supplementary Figure 4. Copy number alterations and allele frequencies across all chromosomes for SMNs**

**Supplementary Figure 5. Germline *TP53* variants in the validation cohort**

Sanger sequencing-derived electropherograms displaying the germline variant in Exon 4 are shown. The three nucleotide codon is shown in color below the single letter amino acid symbol.

**Supplementary Table 1. Treatment exposures and *TP53* Variant status in the Validation cohort**

Tumor, *TP53* variant status (G215C, A639G), and treatment exposure details are shown for each validation sample (VS). “Sequencing failed” indicates samples for which we were unable to establish a genotype due to failure of sequencing reaction.

**SUPPLEMENTARY FILES**

**Supplementary File 1. SNVs for Patient 1’s SMN**

List of somatic single nucleotide variants for Patient 1’s SMN are listed here with details indicating involved gene, chromosomal position, reference and alternative alleles, and type of mutation.

**Supplementary File 2. SNVs for Patient 2’s SMN**

List of somatic single nucleotide variants for Patient 2’s SMN are listed here with details indicating involved gene, chromosomal position, reference and alternative alleles, and type of mutation.

**Supplementary File 3. List of dinucleotide substitutions**

Dinucleotide substitutions for Patient 1’s and Patient 2’s SMNs are listed in the spreadsheet. The chromosome positions, involved gene, and allelic substitutions are indicated.

**Supplementary File 4. *TP53* germline sequencing primers**

Sequences of the primers used for Sanger sequencing of *TP53*. The forward and reverse primer sequences are indicated for each of the sequenced exons.