Supplementary Figure 1: Distribution of osteosarcomas in Osx-Cre;mTmG;p53<sup>fl/fl</sup> and Osx-Cre;mTmG;p53<sup>wm172/fl</sup>. A) Representative images of tumor in different locations with corresponding micro-CT analysis. B) Distribution of tumors in different locations as indicated. C) A Radar graph demonstrating data in B.

Supplementary Figure 2: Extra-skeletal osteosarcomas in spleen and liver. A representative image of extra-skeletal osteosarcomas showing calcified tumor in spleen and liver. No other site of primary tumor was detected.

Supplementary Figure 3: Characterization of calcium deposition, proliferation and p53 accumulation. A) Alizarin Red staining of a primary osteosarcoma tumor and the metastatic site (B). C) Ki67 staining of a primary osteosarcoma. D) Immunohistochemistry analysis of mutant p53 in a primary tumor and higher magnification view of the box area.

Supplementary Figure 4: An IGV Browser snapshot of RNA-Seq generated reads. An IGV browser snapshot comparing the read count of p53-null tumors (Osx-Cre;p53<sup>fl/fl</sup>) with p53 mutant (Osx-Cre;p53<sup>wm172/fl</sup>). The p53R172H mutation is marked as green.

Supplementary Figure 5: Up-regulation of snoRNAs in p53 mutant osteosarcomas. A series of IGV browser snapshots at indicated snoRNA loci.
comparing the expression of indicated snoRNAs with the expression of corresponding host gene’s exon (red box).

**Supplementary Figure 6: Functional Gene Ontology annotations associated with p53R172H mutation.** A bar chart representing the top significant pathways associated with p53R172H mutation signature in osteosarcomas.

**Supplementary Figure 7: Characterization of Ets2 binding at snoRNA’s locus.** A series of IGV browser snapshots at indicated snoRNA loci showing ETS2 occupancy at indicated SNORNA (dark blue).

**Supplementary Figure 8: Rescue of malocclusion phenotype in Osx-Cre mice following Ets2 deletion.** A photograph of teeth malocclusion in Osx-Cre mouse (left) and normal teeth in a Osx-Cre;Ets2^{fl/fl} mouse (right).

**Supplementary Figure 9: Venn diagrams depicting the overlap between genes up or down regulated in Ets2-knockout tumors in comparison to mutant p53.**

**Supplementary Figure 10: Functional Gene Ontology annotations associated with Ets2 loss.** A bar chart representing the top significant pathways associated with loss of *Ets2* in p53 mutant osteosarcoma.
Supplementary Figure 11: Characterization of chromosomal aberrations in p53 driven osteosarcomas.

A heatmap representing the distribution of copy number changes across the genome in p53 mutant as well as null tumors., Amplification, deletion (blue). WFM; metastasizing \( p53^{wm172/fl} \), WFN; non-metastasizing \( p53^{wm172/fl} \), FM; metastasizing \( p53^{fl/fl} \), FNM; non-metastasizing \( p53^{fl/fl} \)

Supplementary Figure 1: Distribution of osteosarcomas in \textit{Osx-Cre;}\textit{mTmG;}\textit{p53^{wm172/fl}} and \textit{Osx-Cre;}\textit{mTmG;}\textit{p53^{fl/fl}}

Supplementary Figure 2: Extra-skeletal osteosarcomas in spleen and liver
Supplementary Figure 3: Characterization of calcium deposition, proliferation and p53 accumulation

Supplementary Figure 4: An IGV Browser snapshot of RNA-Seq generated reads
Supplementary Figure 5: A series of IGV Browser snapshots from different gene loci

Supplementary Figure 6: Functional Gene Ontology annotations associated with p53R172H mutation
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Supplementary Figure 8: Rescue of malocclusion phenotype in Osx-Cre mice following Ets2 deletion.
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Supplementary Figure 10: Functional Gene Ontology annotations associated with Ets2 loss in p53 mutant osteosarcomas
Supplementary Figure 11: Copy number variations in p53 driven osteosarcomas.