One Aggressive Cancer, Two Behaviors: How Genomics Explained Buttercup's Tumor Biology and Treatment Response

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Case Background

Buttercup is a 10-year-old Beagle and initially presented with a cutaneous grade 3 soft tissue sarcoma (STS of the distal left antebrachium, surgically excised on March 19, 2025 with incomplete margins. The mass recurred 10-days after her initial surgery. Buttercup underwent a second surgery for mass removal and lymphadenectomy of left prescapular lymph node on Apr9, 2025 with plan to follow with adjuvant radiation therapy (RT). Histopathology confirmed high-grade STS with no lymph node metastasis, and complete but narrow margins (0.1cm). She developed significant local side effects of grade 2-3 moist desquamation and pain, while still receiving RT. She finished definitive RT on June 4, 2025. On September 9 there was concern about how the site was healing and by October 1, 2025 progressive disease, with tumor regrowing in the radiation field was confirmed.

Amputation was considered but a CT scan of the thorax showed early pulmonary metastases, and additional surgery was cancelled. Buttercup was treated with multiple systemic therapies including metronomic cyclophosphamide (20mg/m2 PO EOD) and Carprofen (2mg/kg PO SID) with continued local tumor progression but minimal change in pulmonary metastasis. Toceranib (2.65 mg/kg PO MWF) was added. Buttercup became progressively painful and amputation was recommended but was declined. The tumor was biopsied for genomic profiling, and intralesional 5-FU was administered without improvement. Three distinct but abutting (maximum diameter 3 cm) tumor masses began to merge forming a nearly circumferential mass around forelimb that was raised with depth of 4.5 cm off of the leg with maximum length (ventral to dorsal) 8.5cm.

Cancer Genomics of the primary tumor and Initial Therapeutic Response

Comprehensive genomic profiling of the primary tumor using Canine CGP identified a subclonal TP53 alteration, along with additional pathway-relevant changes involving STK11 and CIRBP. Based on these molecular findings, five therapeutic options were recommended, including imatinib, vorinostat, sirolimus, carboplatin, and doxorubicin.

Given the TP53-associated biology, the combination of imatinib and vorinostat was prioritized as first-line therapy. Buttercup was started on imatinib (10 mg/kg PO daily) and vorinostat (just over 40 mg/kg every other day) in December 2025. This regimen was well tolerated. On assessment of tolerance 2 weeks of starting imatinib, there was progression noted on January 5th 2026, along with a new 3cm axillary lymph node. Amputation was again discussed but assessment on February 9th showed significant improvement. **The combination of imatinib and vorinostat resulted in a strong and durable response at the primary tumor site, with greater than 50% reduction in tumor burden (depth <1cm with mass contracted to 2/3 of previous width)**

In contrast, the pulmonary metastases continued to progress, with mild enlargement of three existing nodules and the appearance of three new, small metastatic lesions on February 23rd. This discordant response suggested that the metastatic disease was driven by a distinct biological program not adequately addressed by the initial treatment strategy.

Metastatic Biopsy Reveals Clonal Divergence

To explain this discordant clinical response, a lung metastatic lesion was biopsied and profiled in March 2026. Canine CGP demonstrated that the primary tumor and lung metastasis share a common clonal origin, confirming metastatic spread rather than a second independent cancer.

However, the metastatic lesion showed clear evidence of divergent tumor evolution. **While the primary tumor was dominated by a subclonal TP53 mutation, no TP53 alteration was detected in the lung metastasis, indicating that the dominant metastatic clone was TP53-independent.** Instead, the metastatic tumor was characterized by copy number–driven oncogenic signaling, with amplification of multiple cancer-associated genes involved in growth, survival, and signaling pathways, including TFE3, ARAF, and BTK. Based on these findings, sorafenib, trametinib, and ibrutinib were recommended to target the implicated pathways driving metastatic progression.
These findings suggest that TP53-wild-type subclones present within the primary tumor were selectively enriched during metastatic progression, giving rise to lung metastases driven primarily by chromosomal instability independent of TP53 loss.

Biology Explains the Clinical Course

This evolutionary model provides a clear explanation for Buttercup's clinical response:

- The primary tumor responded well to TP53-associated targeted therapy.
- The lung metastases progressed, consistent with a TP53-independent biology that is less sensitive to TP53-targeted treatment.

Precision-Guided Treatment Adaptation

Given the continued clinical benefit at the primary tumor site, imatinib in combination with vorinostat is continued to maintain local disease control. In light of the ongoing progression of lung metastases and their TP53-independent, copy number–driven biology, **sorafenib is added to provide broader pathway inhibition and improved systemic control of metastatic disease.** Buttercup developed diarrhea and Imatinib was altered to 5-days a week dosing with probiotics added. **Thoracic radiographs taken on April 30th 2026 showed a reduction in the size and conspicuity of multiple nodules, although not reaching the threshold of 30% for a true partial response (still early). Buttercup is doing well and has remained non-clinical for her lung metastasis.**

Key Takeaway

Buttercup's case powerfully demonstrates that tumor biology underlies treatment selection and response, and that metastatic progression can emerge through clonal evolution, giving rise to lesions with fundamentally different therapeutic vulnerabilities.

This case underscores the value of precision oncology that enables dynamic adaptation of treatment strategies as tumor biology evolves over time.