FidoCure® Case Study: Missy Martino

Mammary Carcinoma

Dr. Garrett Harvey, VMD
Veterinary Affairs, FidoCure®

Madison Luker, DVM Candidate 2024,
UC Davis School of Veterinary Medicine

After one year of FidoCure® targeted therapy, Missy showed no evidence of pulmonary metastatic disease.

History, Initial Assessment and Surgery

In October of 2018, Missy Martino, a 12 year-old spayed female Chow Mix, presented to the Pet Emergency and Specialty Center of Marin in San Rafael, CA. A mass of approximately 2.0 x 3.0cm was palpated in the region of the first thoracic mammary gland of the right mammary chain. Thoracic radiographs were performed and no evidence of pulmonary metastasis was noted.

Surgical excision of the mass was elected and then performed by the primary veterinarian on October 5, 2018. Histopathology revealed a high grade (grade 3) mammary gland carcinoma with approximately 20 mitotic figures in 10 HPFs. The mass was narrowly excised with neoplastic cells extending to within 4mm and 1mm of the lateral and deep margins, respectively. Subsequently, Missy's family was referred to a veterinary oncologist.

Post-Operative Evaluation and Treatment Plan

On November 12, 2018, a course of injectable chemotherapy doxorubicin (Adriamycin) 25 mg/m2 IV once every three weeks for five treatments was initiated. At a re-staging appointment in April 2019, a new mass was noted on the right ventral thorax near the second mammary gland. Cytologic evaluation confirmed recurrence of mammary neoplasia; thoracic radiographs revealed two small pulmonary nodules and an enlarged sternal lymph node. These findings were consistent with metastatic disease. After discussion of additional treatment options, Missy's family elected to pursue FidoCure® genomic analysis and targeted therapy.

FidoCure® Analysis

Tumor tissue was sent for genomic (DNA) and transcriptomic (RNA) sequencing in May of 2019. Genomic analysis revealed alterations of NOTCH1, CDK6, and KMT2D. NOTCH1 is a transcriptional activator of several genes that play a role in cell differentiation, growth, proliferation and survival. When mutated and constitutively activated, NOTCH1 can contribute to cell cycle progression and tumorigenesis.

CDK6 codes for cyclin dependent kinase 6, which plays a significant role in cell cycle regulation and differentiation. Interestingly, a homologous human CDK6 mutation had been identified in mammary carcinoma with a high pathogenicity score though this mutation was novel/undescribed in dogs (https://cancer.sanger.ac.uk/cosmic).

KMT2D belongs to a large family of lysine methyltransferases. These proteins have primary functions in modulating DNA through chromatin and are frequently altered genes in human cancers. The role KMT2C plays in tumor progression is relatively unclear, though studies have demonstrated a tumor suppressing function in some cancers.

Findings based on RNA expression profiling were consistent with overexpression of CDK4, EGFR, JAK1, MEK1/2, and MYC. CDK4 is the gene encoding cyclin dependent kinase 4. Belonging to the same gene family as CDK6 (above), this protein plays a critical role in cell cycle regulation, and dysregulation of this pathway can play a role in increased proliferation.

EGFR is the gene encoding epidermal growth factor receptor which is a receptor on the cell surface involved in numerous intracellular signaling pathways. Overexpression of this gene may result in tumor cell growth and proliferation through pathways such as MAPK/ERK.

MEK is a gene that codes for the protein MEK1. This is a downstream protein that belongs to the MAPK/ERK signaling pathway. Overexpression of this gene may result in tumor cell growth, proliferation, and survival. Inhibition of MEK1 may reduce effects that this genetic alteration has as a driver of canine cancer.

JAK1 is a gene that encodes a JAK1 protein member of a protein kinase family, activating and recruiting targets such as STAT proteins. The JAK-STAT pathway plays a role in cellular proliferation and tumorigenesis.

MYC overexpression was also noted on the gene analysis. MYC is a gene which codes for intranuclear transcription factors. These proteins are responsible for regulation of various pathways such as cellular growth and proliferation, as well as cellular metabolism.

FidoCure® Treatment

Gene expression results from FidoCure® analysis were received on May 23, 2019 and indicated the potential benefit of using targeted therapies. The following targeted therapies were prescribed by the patient's treating veterinary oncologist:

- Rapamycin (mTOR inhibitor)
  0.1 mg/kg/day PO
- Dasatinib
  0.5-0.7 mg/kg/every other day PO

These medications were administered orally by the pet owners at home.

Imaging performed during recheck examination approximately one year after initiating FidoCure® treatment revealed a large subcutaneous nodule (5.4 W x 5.2 L x 2.6 H) in the ventral thoracic wall. Cytologic evaluation showed features of malignancy, so surgical removal and biopsy were discussed with the pet owner. However, thoracic radiographs performed at this time revealed resolution of the previously described pulmonary nodules and enlarged sternal lymph node identified as metastatic disease.

Conclusion

One year after initiating FidoCure® enabled treatment, Missy showed no evidence of pulmonary metastatic disease.

Missy continued to thrive, maintained quality of life and experienced extended time with her pet parents. Although Missy did develop a subcutaneous nodule (surgical removal and biopsy were considered by the pet owner), there was complete resolution of the pulmonary metastasis and the sternal lymphadenopathy.

What Missy's Parents and Doctor Said

Missy, about 16 years old now, has been a Fidocure® patient for the past year and a half. Diagnosed with advanced mammary cancer for the second time we were unsure what, if any, course to take. We are so happy we chose Fidocure®. She is energetic, eats extremely well, and with few very occasional mild side effects, is enjoying a wonderful life. Also, during her course of treatment the cancer unfortunately metastasized to her lungs. Subsequent X-rays gratefully showed no sign of the lung tumors! Thank you and your team.

— **Joe Martino**, November 2019

I am impressed with the efficacy and results of the treatment and that we have been able to maintain her quality of life while extending her time with her family.

— **Dr. Aarti Sabhlok DVM, DACVIM (Oncology)**, November 2019