Genomic Case Profiles

vidium ANIMAL HEALTH a TGen subsidiary

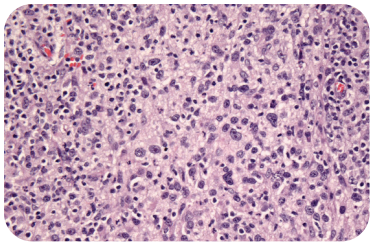
SearchLight DNA™ Guides Treatment Planning

OVERVIEW

- A 10-year-old Golden Retriever was diagnosed with histiocytic sarcoma. After completing an initial course of radiation therapy, medical treatment with cobimetinib was started based on literature suggesting the tumor could bear *KRAS* and *PTPN11* mutations, which are associated with response to cobimetinib.
- A SearchLight DNA™ test revealed the absence of *KRAS* or *PTPN11* mutations along with the presence of a mutation that suggested cobimetinib resistance.
- In Nira's case, Searchlight DNA provided valuable data that informed her treatment plan.

Nira is a beautiful 10-year-old Golden Retriever who developed a mass over her left elbow joint in 2020. This was the same place she had developed a soft tissue sarcoma at age 8, which had been surgically removed and treated with systemic bleomycin and local electrochemotherapy with carboplatin. After the new growth was biopsied, it was diagnosed as a histiocytic sarcoma (HS).

Histopathology



Hematoxylin and eosin (H&E) stain

Histologically, the neoplasm is composed of spindle cells that have large round to reniform nuclei with 1 to 3 prominent nucleoli and exhibit frequent karyomegaly. The background shows moderate numbers of small lymphocytes.

Although lymph node aspirates, chest radiographs, and abdominal ultrasound did not yet reveal signs of disease spread, HS can behave aggressively. Thus, treatment options, including amputation, CCNU, and bisphosphonates, were considered but were not chosen owing to Nira's age (amputation) and limited data supporting improved outcomes for HS (CCNU and bisphosphonates).

In search of other treatments based on literary review, Nira's owner, a pediatric oncologist herself, found in the genomics literature that mutations in the genes *KRAS* and *PTPN11* sometimes occur in HS. Mutations in these genes are very common in Bernese Mountain Dogs (~50%) and somewhat common in Golden Retrievers (~20%). These mutations activate the cancer-promoting MAPK molecular pathway, which can be inhibited with targeted drugs (eg, trametinib and cobimetinib) that have been shown to be effective in human cancers and are being actively studied in canine cancers driven by MAPK pathway mutations. Working with Nira's clinical team at UC Davis, including Drs. Michael Kent and Peter Moore, as well as primary oncologist Dr. Martin Crawford-Jakubiak, therapy was initiated empirically with cobimetinib after an intial course of radiation, based on the published data suggesting the importance of the MAPK pathway in HS.

Next, Vidium was contacted to pursue a genetic diagnosis for Nira. Critically, genomic evaluation of Nira's tumor, including SearchLight DNA™, revealed the absence of *KRAS*, *PTPN11*, or other MAPK pathway mutations, but identified mutations in *TP53*, *PALB2*, *TSC2*, *KIT*, and *PDGFRA*. Additional molecular analyses, such as immunohistochemistry, supported that the MAPK pathway was not activated, that *KIT* and *PDGFRA* protein expression were low, and that the *TP53* mutation was a cancer driver. Given the absence of MAPK pathway activation alongside published evidence that *TP53* driver mutations may render tumors resistant to drugs like cobimetinib, Nira was taken off cobimetinib. After full recovery from her initial radiation therapy, Nira was started on a low dose of adjuvant sirolimus (due to the *TSC2* mutation). Nine months after her HS diagnosis, she is full of life and as happy as can be playing in the tide pools of the Big Island of Hawaii!

If you have a case you would like to share or discuss with our scientists, schedule a consultation.

Schedule a Consultation