CHAPTER 15

Leveraging dogs with spontaneous cancer to advance drug development

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Contents

1 Introduction

Cancer is the most common cause of death in dogs over 10 years of age. The American Veterinary Medical Association estimated that 1.5 million dogs were diagnosed with malignant cancer in 2011 [1], and it is likely that this underrepresents the true incidence today. In addition, the age-adjusted cancer incidence is higher in dogs than in people, with 381–852 cases/100,000 dogs, compared to approximately 300 cases/100,000 people [2]. Many spontaneously occurring cancers in pet dogs closely recapitulate the histology, disease progression and development of drug resistance, spontaneous metastasis, and genetic heterogeneity documented in human cancers. In addition, treatment of cancer in dogs often follows established human

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paradigms including the use of surgery, radiation therapy, chemotherapy, and more recently immunotherapy. As such, spontaneous neoplasia in the dog population provides a unique opportunity to study both tumor biology and novel therapeutic interventions.

Another aspect of the spontaneous canine cancer model that can be useful for elucidating tumor biology relates to the genetic evolution of dogs. As a consequence of breed specific evolution and bottlenecks associated with the generation of individual phenotypes, within breeds there exists striking linkage disequilibrium (LD) that is up to 100× longer in dogs when compared to humans [3]. This reduces the number of single nucleotide polymorphisms (SNPs) required to predict an association within a breed and as such, large genome-wide association studies can be completed with fewer canine samples than would be required if the same study were undertaken in humans. The canine genome also exhibits conserved synteny with the human genome and synonymous germline mutations associated with cancer breed predispositions have been identified [3]. For example, germline mutations in the human cancer predisposition genes *BRCA1* and *BRCA2*, implicated in breast and ovarian cancer, have also been associated with a fourfold increased risk of mammary cancer in English Springer Spaniels [4]. In addition, *TP53* mutations, implicated in Li-Fraumeni syndrome and multiple human cancers, are similarly altered in the germline DNA of canine cancer patients [5, 6]. Other studies have shown homology between dogs and humans in cancer-associated genes, such as *c-met*, *p16, Rb*, and *c-myc* as well as in complex inherited diseases including cardiovascular and neurological disorders. Lastly, known mutations, copy number aberrations (CNAs), chromosomal translocations, and SNPs associated with disease risk are similar in dogs and humans in many cancers, thus identifying regions with shared genomic aberrations for a conserved mechanism of disease pathogenesis.

Traditionally, murine models have been used to model the in vivo biology of tumors and their response to therapeutic intervention prior to the initiation of human clinical studies. Cancer models in mice have typically involved xenografts of human tumors in immunocompromised mice. The genetically engineered mouse models (GEMMs) have certain advantages over xenografts due to the presence of an intact murine immune system and provision of a native environment for tumor growth. However, to develop a GEMM model, it is often critical to know the driver mutation (s), which can create bias [7]. More recently, the evolution of patient-derived xenograft (PDX) models have greatly improved the heterogeneity

of tumor models, but again these mice do not have an intact immune system and some of the known modulators of the microenvironment (cytokines/chemokines) do not work across species, thus limiting microenvironment interactions. In some instances, humanized PDX models have been developed to help more closely recapitulate the human setting, but these have their own challenges [8]. Importantly, while mouse modeling of cancer provides critical information regarding the biology of the disease at both molecular and genetic levels, their utility for assessing therapeutic efficacy prior to human translation has been far less effective, evidenced by the high failure rate of new therapeutic agents. This failure is driven by a multitude of reasons including overestimation of the clinical relevance of short-term tumor responses/tumor growth delay in mice, a lack of comorbidities typically found in human patients, a lower rate of intra- and inter-tumoral heterogeneity, and the inability to accurately predict some toxicities (e.g., emesis does not occur in mice). Dogs, on the contrary, develop spontaneous tumors which often closely recapitulate both the histology and molecular aberrations characteristic of human tumors, thus eliminating the inherent bias generated from mouse xenografts or GEMMs and allowing for better testing and predicting the outcome of experimental therapies [9].

2 Comparative biology and genomics of human and canine cancers

2.1 Sarcomas

2.1.1 Soft tissue sarcoma

Soft tissue sarcomas (STSs) arise from the mesoderm and represent approximately 1% of newly diagnosed cancer in humans. These mesenchymal tumors are generally classified according to the cell of origin, biological behavior, and genomic aberrations, and include liposarcoma, fibrosarcoma (FSA), hemangiopericytoma, and peripheral nerve sheath tumor, among others. Approximately 900–1500 children and young adults are diagnosed with STSs each year; in contrast, approximately 15–30,000 dogs are diagnosed with STSs each year [10]. STSs are highly complex and variable in nature, with the potential for recurrence and distant metastasis [10]. Surgery is the mainstay of therapy in both dogs and humans with STS, with cure rates of up to 85% reported in completely resected human tumors and $<5\%$ recurrence rates in similarly treated canine patients. However, up to 35% of incompletely resected STSs recur in both canine and human patients, and adjuvant radiation therapy is routinely used to help prevent local

recurrence [10]. In both veterinary and human oncology anthracycline-based chemotherapy protocols are commonly utilized to treat STS, however the true role of chemotherapy in extending survival times in the setting of metastatic disease is not well defined. For example, according to a recent study, the median overall survival time in patients with locally advanced/unresectable tumors was only 13–14 months with the use of adjuvant doxorubicin with or without isosfamide [11]. In people these genetically complex cancers can be broadly classified into two major groups, one characterized by chromosomal translocations and the other that shows chromosomal rearrangements including gains or losses [12]. The recurrent chromosomal aberrations have recently been recognized in dogs as well. For example, one study comparing two poorly differentiated FSAs found in Labradors and Golden Retrievers had very similar chromosomal abnormalities with respect to human FSA, including deletions, rearrangements, and chromosomal translocations [13]. These FSAs also demonstrated mutations in *CDKN2A* and *TGFBR1*, associated with a poor prognosis in people [13]. Expression of other molecules implicated in STS in people has also been identified in dogs. The fibroblast growth factor 23 (FGF23) regulates phosphorus metabolism and is expressed in some mesenchymal tumors in people. FGF23 dysregulation has profound clinical implications, with patients experiencing tumor-induced osteomalacia secondary to renal phosphate wasting and low vitamin D3. In a recent study, 31% of canine STS expressed FGF23 in addition to possessing histologic features resembling those observed in analogous human STS [14].

2.1.2 Gastrointestinal stromal tumor

Another sarcoma found in both dogs and people is gastrointestinal stromal tumor (GIST), a tumor that derives from the interstitial cell of Cajal found in the intestinal tract. Mutations in the proto-oncogene *KIT* are found in 50%–80% of affected patients, with additional mutations in the proto-oncogene *PDGFR* found in another 10%–30% [15, 16]. KIT mutations in human GIST consist of activating exon 11 deletions, and analogous exon 11 mutations have been identified in canine GIST patients in approximately 35% of cases [17]. The use of imatinib (Gleevec) in metastatic and inoperable GIST is associated with high objective response rates and it is now routinely used in patients with high risk KIT mutation positive GIST post resection resulting in long-term tumor control [18]. Gleevec has also been used to treat canine GIST with responses reported in dogs [19].

2.1.3 Rhabdomyosarcoma

Rhabdomyosarcoma (RMS), a rare neoplasm affecting both dogs and humans, represents a class of high-grade complex tumors characterized by cellular and morphological variations. The RMS tumors display characteristics of skeletal muscle and express markers of terminal muscle differentiation like MyoD1 and myogenin. RMS in both dogs and humans appears as undifferentiated myoblasts or embryonic myotubes and hence can be commonly misdiagnosed as "anaplastic sarcomas" or "poorly differentiated sarcomas" [20]. The frequency of canine RMS is low, with only 65 total case reports published [20]. In both veterinary and human oncology, RMS is typically classified into four major histologic subtypes: embryonal, botryoid, pleomorphic, and alveolar. Spindyloid RMS has only been recently described in dogs, with a case reported in an 11-month-old boxer dog. Botryoid RMS is the most common subtype in dogs, followed by the pleiomorphic subtype. Botryoid RMS has been reported with increased incidence in the urinary bladder of young, female Saint Bernard dogs [20]. Given the relatively small number of RMS cases that occur in the canine population, a more complete understanding of the genomic similarities and differences between canine and human RMS will be necessary to facilitate comparative clinical trials of novel agents.

2.1.4 Osteosarcoma

Osteosarcoma (OS) is the most common primary bone tumor in both people and dogs, although it is significantly more prevalent in dogs with a reported incidence of >25,000 cases per year compared to <100 per year in people [13]. OS commonly occurs in older dogs (median age 7 years), however a bimodal distribution is present with a small peak in young dogs (average age 1 year). This is in contrast to humans where primarily adolescents are affected [13]. While amputation and adjuvant chemotherapy improves median survival time to 8–12 months, compared to 3–4 months with amputation alone, 90% of dogs are euthanized within 2 years of diagnosis [11]. Similarly, the prognosis for OS in children is guarded; the overall 5-year survival rate is 67% in the nonmetastatic disease setting and 10%–30% if metastases are found at initial diagnosis [13].

OS is a genomically complex tumor, demonstrating both large chromosomal rearrangements and kataegis [21], however it displays similar genetic dysregulation between both species, underscoring the comparative and translational relevance of canine OS to inform the human condition. For example, mutations in *TP53* and *Rb* are among some of the alterations

described in human OS as well as loss of function at the *INK4* locus, amplifications in *CDK4* or mutations in *PTEN* [22]. Similarly, *p53* missense mutations (24%–47%) and copy number loss of *Rb* (29%) have been identified in canine OS. Whole exome sequencing (WES) of human OS implicated the PI3K/mTOR signaling pathway; in addition, somatic CNAs involving the PI3K/mTOR signaling pathway were reported as the second most commonly dysregulated pathway in canine OS [21, 23]. In a study evaluating gene expression across human and canine OS, cluster analysis of orthologous gene expression signatures did not discriminate between the tumors on the basis of species. These data were used to identify overexpression of *IL-8* and *SCL1A3* in canine OS, and to then demonstrate that expression of both is associated with an aggressive clinical course and poor outcome in human OS [24]. Lastly, WES of canine OS across three breeds (Golden retriever, Rottweiler, and Greyhound) identified recurrent somatic point mutations in SETD2 (21%), the sole histone methyltransferase responsible for adding the third methyl mark at histone 3 lysine 36 (H3K36me3) [23, 25]. SETD2 mutations are found in several human cancers, such as renal cell carcinoma and hematopoietic tumors, although with a very low frequency [25, 26]. SETD2 generally functions as a tumor suppressor gene, and in vitro evaluation in human OS implicate SETD2 loss in cell proliferation and survival [27]. Together, these shared genomic similarities in canine and human OS support the use of dogs with OS as a translational model.

2.1.5 Hemangiosarcoma

Hemangiosarcoma (HSA), an aggressive tumor that likely arises from early bone marrow derived endothelial precursors. The human counterpart to this disease, angiosarcoma (AS) is believed to have similar origins [28]. While HSA constitutes 12%–21% of all mesenchymal tumors, AS is rare tumor, with only 100–300 new cases annually [29]. Golden Retrievers, German shepherds, and Labrador retrievers, among others, are breeds at higher risk for developing this cancer. In both dogs and humans, HSA/AS exhibits widespread metastatic behavior that is typically drug resistant, resulting in relatively short lifespans for affected patients despite surgery and chemotherapy (6–8 months for dogs, 14 months for people) [30, 31].

HSA and AS are morphologically and genetically similar, however the low incidence of AS has precluded therapeutic advances. In dogs, genome wide copy number profiling identified several CNAs, also implicated in human AS, including those involving *CDKN2A*, *VEGF-A*, and *SKI* [32]. Constitutive PI3K pathway activation and loss of PTEN expression

have been noted in both AS and HSA [32–34]. In addition, a mutation in *PTEN*, resembling that present in AS derived from a human patient was identified in dogs, and *VEGFA* upregulation has been associated with inactivating mutations in *PTEN* in canine HSA [33]. Another study classified HSA into distinct subtypes based on angiogenesis, adipogenesis, and inflammation gene expression signatures [35]. This study also found distinct expression profiles for early endothelial, hematopoietic, and myeloid cells within the group of tumors analyzed, suggesting that canine HSA arises from multipotent progenitor cells [35].

A recent study in dogs with HSA explored the safety and activity of a novel targeted toxin using EGFR/UPAR (eBAT-EGF-urokinase angiotoxin). In this trial, the 6-month survival rate improved from <40% to approximately 70%, although the 2-year survival rate still remained at approximately 10% [36]. To determine the potential cross-species utility of eBAT, >200 human AS samples and 97 canine sarcoma samples were interrogated, demonstrating significant target overlap between species [36].

2.2 Tumors of hematopoietic origin

2.2.1 Histiocytic sarcoma

Histiocytic sarcoma (HS), first recognized in dogs in the 1970s, is a disorder arising from dendritic cells (interstitial dendritic cells and Langerhans) and macrophages [37]. HS is often associated with multifocal lesions and commonly metastasizes to multiple organs including spleen, lung, liver, and lymph nodes. Histopathology, with or without immunohistochemistry is generally required to rule out other tumor types, such as other round cell tumors or STSs [37]. While HS develops in many breeds of dogs, Flat Coated Retrievers, Rottweilers, and Bernese Mountain Dogs are predisposed, suggesting the involvement of heritable risk factors which contribute to tumor initiation and progression [38]. Treatment generally involves chemotherapy with or without surgery or radiation therapy contingent on the location of the tumor. While up to 46% of dogs with HS exhibit an objective response rate with use of the chemotherapeutic agent lomustine, resistance often develops quickly and most patients succumb to metastatic disease or local recurrence within 6 months [39]. Localized HS is associated with an improved prognosis when treated with lomustine and surgery (median survival time 18 months) [40]. In general, due to the aggressive nature and acquisition of drug resistance by these tumors, the prognosis in dogs with disseminated HS is generally dismal. In humans, HS bears a striking resemblance to the canine disease although it represents a rare diagnosis. There is

no specific age of onset although it primarily affects adults with an associated poor prognosis and high rate of morbidity. As with dogs, HS in people is multifaceted and can affect a variety of organs including skin, bone marrow, GI tract, and the central nervous system (CNS). Despite the use of a multimodal treatment approach involving chemotherapy, radiation therapy, and surgery, outcomes are generally poor [41].

Genomic changes associated with HS in dogs have been interrogated. In one study, comparative genomic hybridization (CGH) identified a large number of recurrent CNAs in 104 tumors from Flat Coated Retrievers and Bernese Mountain Dogs [38]. Recurrent deletions were found in tumor suppressor genes, namely *Rb*, *CDKN2A,* and *PTEN,* as well as a few unique CNAs that potentially contributed to differences in tumor location, onset, and progression [38]. The most highly recurrent CNAs found in the dog tumors were similarly identified in human HS, suggesting a conserved disease evolution. Given the rarity of HS in people, canine HS likely represents a relevant large animal model in which to interrogate novel therapeutic approaches prior to evaluation in subsequent human trials.

2.2.2 Leukemia

In 2017, over 62,000 people were diagnosed with some form of leukemia, and another 24,500 leukemia-associated deaths were reported in the United States alone (American Cancer Society). Leukemia in both dogs and people is subdivided into four major types: acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia, and chronic lymphocytic leukemia (CLL). Acute leukemias are rare in dogs and often rapidly progressive; therefore, they do not represent a good model of the human disease. With respect to chronic leukemias, in humans CLL is the most common form of leukemia as is the case in dogs. Most canine patients with chronic leukemia are asymptomatic and the diagnosis is an incidental finding based on routine bloodwork. In both species, the chronic leukemias may also present with vague signs such as inappetence, splenomegaly, or lethargy. CLL is typically considered an indolent disease, and prognosis is generally determined by age, leukocyte count, and anemia. Other factors influencing prognosis include cytogenetic and molecular aberrations that categorize patients into different risk groups based on subtype [42]. The natural course of CLL is variable however, the reported median survival time is approximately 10 years in people and 16–31 months in dogs. The most common form of CLL in adults arises due to a clonal proliferation of CD45+ B-cells; in contrast, dogs typically develop CD8+ T-cell disease [43, 44].

Interestingly, despite differences in immunophenotype, CLL in both species exhibits deletions in the *RB1* locus and subsequent reduced or absent Rb protein expression [45, 46].

In humans, CML is characterized by an aberrant *BCR-ABL* transcript secondary to a reciprocal translocation between the breakpoint cluster region (*BCR*) located in 22q11 and the *ABL* oncogene located in 9q34 (ABL locus), also known as the "Philadelphia Chromosome" [47]. The BCR-ABL translocation results in constitutive activation of the cytoplasmic kinase ABL, driving tumor cell growth [47]. Although CML is an uncommon diagnosis in dogs, fluorescence in situ hybridization identified a BCL-ABL fusion protein analogous to the Philadelphia chromosome, known as "Raleigh Chromosome" in >40% of dogs affected by this disease [45]. The comparative genomic studies between canine and human chronic leukemias support the presence of shared disease drivers and the future inclusion of dogs with chronic leukemia into the drug discovery and development process.

2.2.3 Lymphoma

Lymphoma is a heterogeneous group of hematopoietic tumors with clinically and molecularly distinct subtypes. It is common in people, accounting for approximately 5% of all cancers [22]. Non-Hodgkin lymphoma is the most abundant subtype, with a SEER age-adjusted incidence of 19.4 new cases of people per 100,000 at risk in 2018. The incidence of lymphoma is higher in dogs, with a rate of 15–30 new cases per 100,000 dogs/year, although recent data indicate that the incidence is increasing [48]. The distribution of B-cell and T-cell lymphomas in dogs mirrors that in people, with B-cell neoplasia occurring in 60%–65% and 75%–80% of cases, respectively [49]. In addition, diffuse large B-cell lymphoma (DLBCL) is the most common subtype in both species. With respect to T-cell neoplasia, the two most common subtypes in dogs are high-grade T-cell (peripheral T-cell not otherwise specified; PTCL-NOS) and low-grade T-zone lymphoma (TZL). Similarly, PTCL-NOS is the most common subtype of T-cell lymphoma in people, with TZL generally categorized as a component of PTCL-NOS. Dogs also develop other subtypes of lymphoma found in people, thus providing a good comparative resource to dissect the molecular and genomic drivers of disease [49]. For example, genome-wide expression analysis across six histologic subtypes of canine lymphoma identified distinct markers predictive of subtype and patient outcome in both T- and B-cell diseases [50]. As with other cancers in dogs, breed-specific susceptibility

to different types of lymphoma is recognized, implying the existence of heritable risk factors. Rottweilers develop B-cell lymphoma exclusively, Golden retrievers develop B-cell and T-cell lymphomas with equal frequency, and over 90% of lymphoma cases diagnosed in Boxer dogs are of T-cell origin [49].

In people, DLBCL is typically categorized into two prognostic groups based on genetic signatures: activated B-cell (ABC) and germinal center B-cell (GCB). Although these specific signatures are not found in canine DLBCL, ABC-like, and GCB-like molecular subtypes have been characterized, with many canine tumors possessing high Myc and Bcl2 expression concordant with the double hit phenotype found in people [51]. Additional similarities include activation of the NF-κB pathway and ongoing somatic hypermutation (SMH) in the immunoglobulin heavy chain [51]. Most human DLBCL cases have completed SMH prior to lymphomagenesis, indicating that they have passed through the germinal center. However, high intraclonal variability in a subset of human DLBCL cases supports the presence of ongoing SMH, which is associated with GCB-DLBCL and an improved prognosis. Importantly, the presence of SHM in canine DLBCL also predicts patient outcome, demonstrating that shared molecular aberrations are associated with similar disease biology [51]. In support of this, a pilot study in dogs with ABC-DLBCL showed that NF-κB inhibitors could safely be administered, resulting in downregulation of B-cell proliferation [2]. Another gene dysregulated in both canine and human B-cell neoplasia is TRAF3, which encodes a negative regulator of NF-κB. RNA sequencing/exome sequencing identified inactivating mutations in 44% of canine B-cell LSA tumor samples after which human DLBCL samples were interrogated, where loss of TRAF3 expression was found in approximately 9% of patients [52]. Lastly, evaluation of shared copy number gains in canine chromosome 13 (CFA 13) and syntenic regions of human chromosome 8 (HSA 8) involving the *MYC* locus were identified in lymphoma samples using array CGH (aCGH) [53]. The investigation of conserved cytogenetic rearrangements involving the *MYC* oncogene in both canine and human lymphoma facilitated fine resolution mapping, underscoring the utility of comparative cancer research to identify driver mutations across species with improved resolution [45].

With respect to comparative genomics of canine and human T-cell lymphomas, recurrent somatic mutations involving *MET*, *KDR*, *STK11*, and *BRAF* were identified in dogs, classifying novel mutations and demonstrating similar pathway aberrations when compared to human T-cell lymphoma

[54]. In addition, WES of T-cell lymphomas from Boxer dogs, a breed predisposed to aggressive T-cell lymphoma, identified mutations in *PTEN* in 25% of cases [55]. The clinical utility of targeting the PI3K/Akt axis was recently described in a phase I/II clinical trial in which dogs with lymphoma were treated with a novel PI3Kδ inhibitor, RV1001. A 68% objective response rate (complete and partial responses) was observed in dogs with T-cell lymphoma [56]. Notably, similar response rates following RV1001 therapy occurred in B-cell and T-cell patients, underscoring the importance of considering molecular context of disease for optimization of translational research efforts.

In both species, multiagent chemotherapy protocols serve as the basis for treatment, with the CHOP protocol most commonly used [57]. The shared disease biology and clinical features of canine lymphoma have long been an attractive model to study and optimize therapeutic approaches prior to human trials. Notably, the seminal work utilizing autologous and allogeneic bone marrow transplants in healthy dogs and dogs with lymphoma demonstrated that canine patients could undergo the transplantation procedure and achieve complete hematologic reconstitution and clinical benefit. This laid the foundation for subsequent successful human bone marrow transplantation trials [49].

2.3 Carcinomas

2.3.1 Transitional cell carcinoma

Transitional cell carcinoma (TCC) is the most common primary tumor of the urinary bladder in both dogs and people. While TCC is typically classified as low-grade superficial carcinoma in people, canine TCC presents as a high-grade infiltrative tumor that closely recapitulates many of the salient features of high-grade human TCC, including histologic classification, response to treatment, and development of metastatic disease [58]. While <15% of canine patients present with metastasis at diagnosis, spread to regional lymph nodes and distant sites, including the lungs and bone, is observed in 50% of human and canine TCC patients at the time of death [58]. Several breeds of dog are predisposed to TCC, including Scottish terriers, West Highland White Terriers, and Shetland sheepdogs. Treatment of TCC in people commonly involves surgery (complete cystectomy) and chemotherapy. Surgical resection of TCC is less common performed in dogs due to the morbidity associated with total cystectomy and the frequency in which tumors present in the trigone with urethral and/or prostatic involvement. Chemotherapy and cyclooxygenase inhibition are the

mainstay for therapy of canine TCC, however, the therapeutic benefits are relatively low, with only 30% of patients achieving substantial benefit [58].

Several shared molecular and cellular alterations have been identified in TCC, including HER-2, survivin, basic fibroblast growth factor, and cyclooxygenase (COX)-2 overexpression as well as telomerase activity [58]. COX-2 has been extensively studied in both canine and human TCC. Notably, the clinical utility of COX inhibition in TCC was first demonstrated in dogs, prior to its subsequent evaluation in people with similar clinical benefit achieved in both species [59, 60]. The role of both androgen and estrogen receptors (AR and ER) has been interrogated in bladder cancer. Several studies have demonstrated that loss of AR signaling is associated with an increased grade and stage of disease in human TCC. Similarly, AR downregulation was observed in high-grade canine TCC [58]. While there is some debate regarding the role of ERα and ERβ in human TCC, ERβ is typically associated with high-grade/high-stage tumors with a poor outcome after cystectomy [58]. ER expression is present in the majority of canine TCC samples, however, ER expression is also commonly noted in normal bladder tissue, highlighting the importance of evaluating hormone receptor expression in intact dogs as well as spayed/neutered animals.

Recently, *BRAF* V600E mutations, analogous to those commonly found in human malignant melanoma/thyroid carcinoma/colon carcinoma, were identified in over 80% of canine invasive TCC cases [61]. While *BRAF* mutations are rarely identified in human urothelial tumors, their high prevalence in the canine disease supports the notion that molecular aberrations driving cancer can transcend histology. As such, canine TCC may serve as an excellent model of *BRAF* mutation in the context of carcinomas.

2.3.2 Mammary tumors

Mammary tumors are the most common tumor reported in female dogs, with a recent European study reporting an incidence of over 600 cases per 100,000 dogs [62]. Known risk factors for their development include hormonal influences, breed, age, obesity, and possibly diet [2]. The prognosis for dogs with mammary tumors is dependent on the tumor grade and stage of the disease, however recent studies have investigated the utility of immunohistochemical markers, in addition to comparative expression analysis of orthologous canine/human genes, identifying similar prognostic gene signatures [63].

Mammary tumors (breast cancer) in people are classified according to the presence or absence of prognostic and therapeutically relevant molecular

markers and gene expression profiles. Luminal A and Luminal B subtypes are estrogen receptor (ER)-positive, while ER-negative subtypes include HER-2 overexpressing, normal breast-like, basal-like, and claudin-low. The basal-like and claudin-low subtypes are generally characterized by the lack of HER2, ER, and progesterone receptor expression (i.e., triple negative breast cancer). While this classification scheme is not routinely utilized in clinical veterinary medicine, similar molecular, and hormone receptor expression aberrations are recognized in both canine and human mammary tumors. For example, hormone receptor (ER and PR) positivity is associated with an 85% 1-year survival in canine mammary tumors. In contrast, hormone receptor negative tumors analogous to basal-like tumors (ER negative, HER2 negative, and negative for basal markers) have been identified in up to 24% of canine mammary carcinomas. Additionally, epidermal growth factor-2 (*HER2*, *ERBB2*), a proto-oncogene overexpressed in approximately 25% of canine and human breast cancers, is associated with a poor prognosis in both dogs and people [2]. Lastly, an inverse relationship between E-cadherin expression and Sialyl Lewis X (sLe^X) has been found in tumors from both species; loss of E-cadherin and upregulation of sLe^X is associated with a poor prognosis in human breast cancer and increased lymph node metastasis in canine mammary tumors [64].

With respect to genetic drivers of disease predisposition, mutations in the BRCA tumor suppressor gene family are linked to both ovarian and breast cancer in women [65]. Concordant with this data, SNPs in both *BRCA1* and *BRCA2* have been associated with mammary tumor development in English Springer Spaniels, a breed predisposed to this cancer [4]. More recently, 97.9% of intact female dogs were reported to have up to 3 polymorphisms in exon 11 of the *BRCA2* gene, supporting a correlation with mammary tumor predisposition [66]. Somatic *BRCA2* SNPs have also been associated with double stranded DNA break repair through RAD51 in canine mammary tumors [67].

Finally, mounting evidence indicates that the tumor microenvironment plays a crucial role in the disease biology of breast cancer in people. Gene expression signatures of laser-captured cancer-associated stromal tissue from canine mammary tumors demonstrated similarities in cancer-associated stromal tissue markers, including *αSMA* and *COL1A1*, between the two species [68]. In people, mammographic density correlates with the presence of collagen-rich tissue and is a known risk factor for breast cancer development. Similarly, collagen density and three-dimensional structure correlated with overall survival time and tumor grade in canine mammary carcinomas [69].

Inflammatory mammary tumors are a rare and highly aggressive type of breast cancer in both people and dogs, with a reported incidence of 3%–11% and 7.6%, respectively [70]. It is typically characterized by tumor cell invasion of dermal lymphatic vessels as well as elevations in serum inflammatory cytokines (IL-10, IL-8) which is associated with an increased presence of CD14+ tumor-associated macrophages. The higher incidence of mammary tumors in the canine population in addition to similar disease biology and molecular aberrations support their use as a translational model.

2.3.3 Squamous cell carcinoma

Squamous cell carcinoma (SCC) occurs most commonly in the oral cavity of dogs, representing the second most commonly diagnosed malignant tumor in this location. The incidence of canine nontonsillar SCC is 6.4–7.3 per 100,000 dogs [71]. The average incidence of human head and neck cancer squamous cell carcinoma (HNSCC) is similar, estimated at 8.8 and 5.1 per 100,000 men and women, respectively [72]. Environmental risk factors (alcohol consumption and smoking) and human papillomavirus infection are known driver of human HNSCC. In contrast, while papillomavirus DNA has rarely been isolated from canine SCC tumor samples, there is no association between p16 immunostaining and papillomavirus DNA, suggesting that infection does not play a role in the canine disease [73]. In both species, HNSCC is highly invasive, with late metastasis to regional lymph nodes and lungs. With respect to the genomic landscape of canine SCC, aCGH, and RNA sequencing revealed CNVs, mutational patterns and altered cellular pathways (cell cycle, TGF-β, PI3K, AKT) analogous to those found in humans [71]. As with human HNSCC, genes regulating the epithelial-mesenchymal transition (TWIST1 and SNAIL) and matrix metalloproteinases were also overexpressed in the canine tumors [71].

SCC is one of the most common malignant tumors of the digit in dogs. An increased risk has been reported in several dog breeds, including standard poodles with a dark coat color. A GWAS study in standard poodles with digital SCC mapped a significant SNP to the *KIT Ligand* (*KITLG*) locus [74]. However, while both light and dark colored standard poodles carry the risk allele, only dark colored poodles are susceptible to digital SCC. The *melanocortin 1 receptor* (*MC1R*) locus was identified as the only difference between light and dark colored poodles, suggesting a protective aberration in *MC1R* in light colored poodles [74]. *KITLG* and *MC1R* are both pigment-associated genes, and *MC1R* variants have been associated with hair color and nonmelanoma skin cancer risk in people [75]. In addition,

KIT ligand has been associated with colorectal and testicular carcinomas in people, supporting the notion that studying breed-associated traits can help identify multigene interactions important in tumorigenesis [76, 77].

2.3.4 Gastric carcinoma

Gastric carcinoma (GC) is relatively rare in dogs, representing only 0.1%–0.5% of all canine neoplasms; 80%–90% of these tumors are adenocarcinomas [78]. An increased prevalence of GC exists within certain dog breeds including Tervueren shepherds, Bouvier des Flandres, Groenendael, and Collies, suggesting a genetic component to the disease [79]. GC is more prevalent in people than dogs, likely due to the influence of environmental risk factors (smoking, alcohol consumption, diet), genetic factors, and *Helicobacter pylori* (*H. pylori*) infection [79]. *H. pylori* causes chronic inflammation, genetic and epigenetic changes, all of which promote carcinogenesis. Although *H. pylori* infection is thought to be a risk factor for feline GC, a relationship between *H. pylori* and GC has not been established for dogs [79]. GC in both species is often diagnosed in the later stages of disease with over 50% of patients presenting with metastasis [78]. While early diagnosis and resection can be associated with a favorable prognosis, despite aggressive treatment, the overall outcome for human patients is poor, with $<10\%$ surviving 5-years [79]. Similarly, most canine patients succumb to GC within 6 months, due to postoperative disease recurrence or metastasis.

HER-2 is an important prognostic biomarker and therapeutic target in human GC, and other predictive biomarkers (HER-3, c-Met, PD-1) have been investigated [80]. Similarly, HER-2 and EGFR overexpression has been documented in 57.9% and 42.1% of canine GC, respectively. In addition, HER-3 and CDX-2 (a nuclear transcription factor often utilized as a marker of human GC) overexpression were documented in both primary tumors and metastatic lymph nodes from canine patients [81]. The C2-O-sLe(X) [Sialyl Lewis x-modified core 2 branched O-glycan; sLe(X)], a carbohydrate tumor antigen present in over 50% of canine GCs, is associated with anaplastic tumors and plays a possible role in tumor cell invasion and metastasis [78]. Similarly, sLe(X) is expressed in over 50% of human GC cases, and correlates with tumor stage and prognosis [82]. Lastly, approximately 75% of human GC with evidence of microsatellite instability have concurrent KRAS mutations; when present together they are associated with a poor prognosis [83]. Although KRAS mutations were found in only 7% of canine GC samples, they point to a possible shared genomic driver that may promote resistance to HER-2 targeted therapies [84].

2.4 Other tumors

2.4.1 Malignant melanoma

Exposure to UV radiation is a primary causal factor for the development of malignant melanoma in people, however nonsun induced melanoma still occurs in a considerable number of individuals [85]. In dogs, malignant melanoma is generally not considered to be UV-induced, and typically occurs in the oral cavity, with melanoma of the digit and skin occurring less frequently [85]. In both species, malignant melanoma exhibits substantial resistance to chemotherapy, but is susceptible to immunotherapy. Melanoma in dogs and humans shares numerous clinical and histopathological features. For example, canine melanoma can be classified using genes typically associated with human melanoma. Specifically, *PTEN* and *NRAS* mutations at known hotspots were identified in canine melanoma samples [86].

The *BRAF* V600E mutation is regarded as a driver mutation in up to 60% of human dermal melanomas, although it is rarely found in the canine melanoma [87]. Interestingly, dysregulated PI3K/AKT and MAPK signaling has been identified in both human and canine melanoma [88]. A common driver of PI3K/AKT and MAPK signaling is *NRAS*, which is frequently mutated in human cutaneous melanoma. In contrast, *NRAS* mutations are rare in mucosal melanoma, reported in <30% of cases in both species. The paucity of *NRAS* and *BRAF* mutations in oral melanoma supports the idea that melanomas that arise in different anatomic locations are driven by distinct genomic changes. Finally, up to 50% of canine oral melanomas express the KIT protein, although activating mutations are not documented [88]. However, the presence of KIT expression correlates with survival in dogs. In contrast, activating mutations in KIT are found in 16% of the oral and 23% of the acral human malignant melanomas [88]. The low frequency of BRAF mutations in combination with similar signaling pathway and kinase alterations in canine melanoma is analogous to the BRAF wild-type status in human mucosal melanoma, supporting the utility of the canine disease as a spontaneous model for the non-UV-associated human melanoma.

2.4.2 Glioblastoma multiforme

Glioblastoma multiforme (GBM), also known as grade IV astrocytoma, is the most common primary malignancy occurring in the CNS. In humans, it accounts for 12%–15% of CNS tumors and approximately 50% of all astrocytomas. In older patients, primary GBM arises without any prior

histological or clinical evidence of a low-grade glioma while secondary GBM progresses from low-grade glioma and typically affects younger patients. GBM can be classified into four grades: grades I and II are slow growing, less aggressive tumors, while grades III and IV are malignant tumors characterized by a high proliferation rate and aggressive biologic nature [89]. Standard treatment commonly consists of surgery followed by radiation therapy and adjuvant temozolomide, although the prognosis for most affected patients is grim [89].

In dogs, glial tumors are the second most common primary brain tumor, and include astrocytomas, oligodendrogliomas, and GBM. GBM accounts for approximately 5% of astrocytomas, which represent 10% of all canine brain tumors [90]. Brachycephalic breeds, such as Boxers, Bulldogs, and Boston terriers, are at increased risk for developing GBM. As in people, the spectrum of gliomas ranges from low-grade slow-growing tumors to poorly differentiated GBM. Similar to the case in humans, canine GBM has a relatively dismal prognosis, with early relapse following surgery and radiation therapy. Several similarities to human GBM have been reported including changes in chromosomal instability, specific gene arrangements, the presence of tumor stem cells, expression of growth factors and their receptors such as EGF, PDGF, VEGF, as well as other frequently described markers such as IL-13Ra2, IGFBP2, and telomerase [91].

It is important to note that unlike with murine models of GBM, the canine disease offers an opportunity to longitudinally monitor patients during therapy, permitting repeat imaging, tumor sampling, and pharmacokinetic/pharmacodynamic assessments. Furthermore, as canine GBM develops in the context of an intact immune system, the immune microenvironment more closely recapitulates that found in human GBM [91]. This has been leveraged for exploration of novel immunotherapies including delivery of adenoviral vectors encoding human FLT3L-generated dendritic cells and autologous tumor cell vaccines combined with CpG oligodeoxynucleotides, both of which demonstrated immune modulation and associated clinical responses in dogs with primary brain tumors [92].

3 Incorporation of canine cancer trials into therapeutic development

3.1 Clinical trials in pet dogs with cancer

.While the use of dogs with spontaneous cancer to study innovative therapeutic approaches for cancer is not new, such clinical studies are increasingly

being incorporated into the translational paradigm. For example, the limb sparing techniques used today in the treatment of OS were first optimized in dogs with OS. In addition, dogs have been successfully employed to provide preclinical evidence supporting the use of liposome encapsulated muramyl tripeptide phosphatidyl ethanolamine (L-MTP-PE; mifamurtide). While no improvements in progression free survival were observed with the use of adjuvant L-MTP-PE in subsequent testing in pediatric patients with OS, overall survival was significantly improved [93]. These studies ultimately resulted in approval of L-MTP-PE in Europe in 2008 for the treatment of newly diagnosed nonmetastatic OSA in conjunction with chemotherapy.

The Comparative Oncology Program (COP) operating within the Center for Cancer Research at the National Cancer Center was established over 10 years ago to support an infrastructure of activities aimed at leveraging canine cancers to accelerate and optimize human drug development. The COP founded its associated Comparative Oncology Trials Consortium (COTC), a network of now over 20 extramural academic comparative oncology centers dedicated to the design and conduct of clinical trials involving novel therapeutics with comparative and translational value. Studies performed through the COTC provide key pharmacokinetic and pharmacodynamic data that can be used to guide subsequent human trial efforts. In addition, the multiinstitutional nature of the COTC permits rapid patient accrual and timely attainment of study endpoints. For example, a recent phase 3 study designed to evaluate the value of adjuvant rapamycin in dogs with microscopic metastatic OS enrolled over 300 patients in 2 years, generating a large clinical dataset in addition to a substantial set of well-annotated biospecimens for future interrogation. The COTC Pharmacodynamic core is an extension of the COP, providing the infrastructure to support rapid assessment of pharmacodynamic and biologic endpoint assessments associated with COTC-supported clinical trials. In addition to resources associated with the COP, there are several other organizations that support multiinstitutional veterinary trial efforts, such as the CTSA One Health Alliance (COHA, https://ctsaonehealthalliance.org).

3.2 Incorporation of canine clinical trials in pre- and post-IND work

The process of drug development, from inception to market approval, can take well over 10–15 years, often costing over a billion dollars. This high cost is due, in part, to the relatively low success of drugs that make it through the

pipeline to full approval, with failure rates approaching 80%–90%. The drivers of this high failure rate are multifactorial and are likely due in part to the heavy reliance of cancer models that do not truly recapitulate the natural history of human cancers, are undertaken along accelerated timelines, do not have the capacity to predict many toxicities and often do not incorporate an intact immune system. Importantly, no one single model can accurately mirror the breadth of heterogeneity within human cancers, particularly with respect to the existing comorbidities that invariably influence outcomes. As such, there is a critical need for preclinical models that can add value to the existing framework of cancer drug development. While not all spontaneous canine cancers are direct correlates of their human counterparts, there are often enough similarities with respect to clinical presentation, molecular abnormalities, and genomic changes that provide a sound basis for their use as a translational model. In addition, their large size permits longitudinal interpatient evaluations that are typically not possible in rodent models. This includes serial imaging, tissue sampling, and quality of life assessment, an important endpoint that impacts human trials. Lastly, as there are no mandated standards of care as is the case in human medicine, clinical trials in dogs with cancer can more readily enroll untreated patients, which may provide valuable information regarding therapeutic activity in the setting of naïve disease that would not otherwise be noted in heavily pretreated patients.

Clinical trials in dogs with cancer have been used to support both pre- and post-investigational new drug (IND) applications for a variety of therapeutics. These are generally supported by data generated from healthy laboratory dogs, facilitating the transition to affected patients by providing an initial assessment of dose, pharmacokinetics/pharmacodynamics and expected adverse events. In the pre-IND setting, the canine studies are typically used to establish safety, demonstrate target inhibition, and provide a signal of biologic activity. In the post-IND setting, the studies can help to optimize dose/regimen and explore combination therapies among others. Several examples of these are provided below:

3.2.1 COTC studies

The first COTC-run clinical trial evaluated an AAV-phage vector that delivered tumor necrosis factor (RGD-A-TNF) to the tumor endothelium [94]. This study validated the utility of the COTC infrastructure to efficiently provide essential preclinical data, including target specificity and safety, to inform the development of future human clinical studies. Since

then, multiple studies have been undertaken by the COTC, including evaluation of novel therapeutic agents and proof-of-concept molecular trials to aid clinical decision making. For example, the camptothecin class of drugs (irinotecan and topotecan) are currently the only approved topoisomerase 1 (TOP1) inhibitors approved by the FDA but chemical instability, drug efflux mediated resistance, and diarrhea limit their utility warranting the development of novel TOP1 inhibitors. The COTC led a multicenter clinical trial in 84 dogs with lymphoma to evaluate the efficacy, pharmacodynamics/pharmacokinetics and toxicity of three indenoisoquinoline non-camptothecin TOP1 inhibitors (LMP400, Indotecan; LMP776, Indimitecan; and LMP744) each of which had been previously studied in mouse models [95]. Sustained tumor accumulation, γH2AX induction, and TOP1 reduction in tumor samples were observed for the lead compound LMP744, and these associated with objective response to therapy in 68% of dogs. Importantly, data from this clinical trial supported the initiation of a Phase 1 clinical trial of LMP744 in people with relapsed/refractory cancers, demonstrating the impact of COTC generated data on human oncology therapeutic development.

3.2.2 Toceranib phosphate and sunitinib malate

Toceranib phosphate (Palladia, Zoetis) and sunitinib malate (Sutent, Phizer) are both orally bioavailable multitargeted small molecule inhibitors with activity against VEGFR, PDGFR, and KIT, originally co-developed by Sugen, Inc. Prior to clinical evaluation of sunitinib, toceranib was studied in dogs with spontaneous cancer to define the pharmacokinetic/pharmacodynamic relationship and determine biologic activity and safety of the drug. In a phase 1 study of toceranib including dogs with a variety of spontaneous tumors, 28% of dogs experienced an objective response to treatment [96]. Subsequent phase 2 and 3 clinical trials were performed in canine mast cell tumors (MCT) that often express activating KIT mutations [97]. Together, these studies established the drug safety profile, pharmacokinetic/pharmacodynamic endpoints, and correlation of activity to KIT mutation status. Specifically, the objective response rate for dogs receiving toceranib was 42.8%, and MCT bearing activating KIT mutations were more likely to have a complete response compared to KIT-mutation negative tumors [97]. The studies in dogs were performed prior to the phase 1 evaluation of sunitinib in people, and helped position sunitinib for evaluation in human patients with imatinib resistant KIT mutation positive GIST. Sunitinib received FDA approval in 2006 for the treatment of advanced renal cell carcinoma

and imatinib-resistant GIST. Subsequent to this, toceranib received FDA approval for the treatment of MCTs in 2009.

3.2.3 Ibrutinib and acalabrutinib

Ibrutinib (Imbruvica, Pharmacyclics LLC) and acalabrutinib (Calquence, AstraZeneca) are Bruton's tyrosine kinase (BTK) inhibitors, approved for use to treat B-cell malignancies. BTK is a kinase downstream of the B-cell receptor associated with proliferation and survival. Ibrutinib was initially evaluated in dogs with B-cell lymphoma where objective responses and safety were demonstrated, in addition to high levels of target inhibition [98]. Ibrutinib received FDA approval for the treatment of mantle cell lymphoma in 2013, and over the next 4 years was subsequently approved for the treatment of CLL, Waldenstrom's macroglobulinemia, small cell lymphocytic lymphoma, marginal zone lymphoma and chronic graft versus host disease. Dogs with spontaneous B-cell lymphoma were subsequently used to evaluate a second-generation BTK inhibitor, acalabrutinib, prior to clinical studies in people. In this phase I clinical trial acalabrutinib was shown to be both safe and efficacious, with an objective response rate of 25% [99]. Importantly, twice daily dosing was associated with improved clinical responses and BTK occupancy, a finding not predicted by prior preclinical modeling, helping to guide dosing in the subsequent human trials. Acalabrutinib received FDA approval for people with mantle cell lymphoma in 2017.

3.2.4 Verdinexor and selinexor

Selinexor (KPT-330) and verdinexor (KPT-335) are both orally bioavailable small molecule inhibitors that reversibly block nuclear export protein XPO1 (CRM1) that regulates movement of key tumor suppressor proteins/growth regulatory proteins between the cytoplasm and nucleus. Aberrant localization of these proteins is associated with poor prognosis in many tumors supporting the notion that XPO1 contributes to tumorigenesis and therapeutic resistance [100]. Verdinexor was evaluated in dogs with spontaneous cancers prior to the initiation of clinical trials of selinexor in people to validate pharmacokinetic/pharmacodynamic relationships, tolerability, and biologic activity. In phase 1 and 2 trials of verdinexor in dogs with lymphoma, over half of dogs derived clinical benefit, with toxicities primarily observed in the gastrointestinal tract (anorexia, weight loss) [100]. These data were included in the selinexor IND application and ultimately predicted activity and toxicity in human patients. Selinexor was recently

granted Fast Track designation approval for the treatment of multiple myeloma demonstration of activity in the setting of pentarefractory disease.

3.2.5 Tenalisib and RV1001

Dogs with lymphoma have also been used to evaluate phosphatidylinositol 3-kinase (PI3K) inhibitors which drive downstream signaling through AKT and mTOR. The RV1001 is an orally bioavailable inhibitor of the PI3Kδ isoform, the expression of which is typically restricted to hematopoietic cells. Phase 1 and 2 clinical trials of RV1001 in canine lymphoma validated target inhibition, established pharmacokinetic/pharmacodynamic relationships, tolerability, and activity of the drug [56]. The combined objective response rate was over 70% and both naïve and refractory disease appeared to derive nearly equal benefit from treatment [56]. Importantly, these data demonstrated significant activity in the setting of T-cell lymphoma which supported the evaluation of a similar drug, the PI3K γ/δ inhibitor Tenalisib (RP6530) in the setting of human peripheral and cutaneous T-cell lymphoma.

3.2.6 KTN0158

Dogs with MCTs were used to evaluate a humanized anti-KIT monoclonal antibody, KTN0158. This monoclonal antibody did not bind to mouse KIT but exhibited strong binding to canine, primate, and human KIT. KTN0158 was first studied in healthy dogs to confirm target specificity, KIT modulation in vivo, and safety, then was studied in a phase 1 study in dogs with MCTs where KIT is a known driver. Clinical benefit of KTN0158 administration in dogs with MCT ($n=5$ partial response; $n=7$ stable disease) was observed regardless of *KIT* mutation status, and decreased KIT phosphorylation was demonstrated in tumor samples. Histopathology after study completion demonstrated an absence of neoplastic cells in the primary tumors and/or metastatic lymph nodes from four dogs [101]. Importantly, this clinical trial established the safety profile and dose-limiting toxicities of KTN0158, supporting subsequent initiation of phase 1 studies in human GIST, another KIT driven malignancy.

3.2.7 STA-1474

STA-1474 is a water-soluble pro-drug of the heat shock protein 90 (HSP90) inhibitor, ganetespib (STA-9090). Both in vitro and murine xenograft studies in a variety of tumor cell lines including those derived from canine cancers demonstrated potent activity in the nanomolar range, supporting

evaluation in dogs with spontaneous tumors [102]. A phase 1 trial of STA-1474 in dogs demonstrated that objective response to therapy was associated with sustained blood levels of STA-9090 between 200 and 600 ng/mL for 8–10 h, a correlation not predicted by the preclinical murine models [103]. Upregulation of HSP70 was observed as a marker of HSP90 inhibition in both tumor tissue and peripheral blood mononuclear cells. Notably, a subsequent evaluation trial of STA-1474 in dogs with MCT using KIT expression as a biomarker for HSP90 activity was undertaken to define a treatment regimen that provided sustained downregulation of client protein expression. In KIT or EGFR-driven murine tumor models, drug administered on Days 1 and 2 (D1/D2) demonstrated increased biologic activity compared to D1 treatment alone. In dogs with MCT, D1/D2 dosing was associated with sustained KIT downregulation, 50% objective response rate and 100% clinical benefit rate compared to D1 and D1/D4 schedules [104]. These data demonstrate the utility of canine correlative trials to help define pharmacokinetic and pharmacodynamic relationships and use this information to identify treatment regimens associated with superior biologic activity.

4 Conclusions

The high rate of cancer in dogs combined with shared molecular and genomic features when compared to analogous human cancers provides a unique opportunity for incorporating comparative clinical trials into the translational paradigm. Given the relatively high failure rate of oncology drug development and the associated high cost of human trials, studying novel therapies in dogs with cancer can help to optimize choice of histology, establish dose/regimen, and better predict drug related toxicities, especially in the setting of comorbidities. Together, this would serve to optimize trial design prior to the initiation of human studies, thereby improving the likelihood of subsequent therapeutic success.

Abbreviations

ACI Animal Clinical Investigation
ALL acute lymphoblastic leukemia
AML acute myeloid leukemia
AS angiosarcoma
BCR breakpoint cluster region
BTK Bruton's tyrosine kinase
CB clinical benefit

CCOGC Canine Comparative Oncology and Genomics Consortium
CLL chronic lymphocytic leukemia
CML chronic myeloid leukemia
CNA copy number aberration
CNS central nervous system
COP Comparative Oncology Program
COTC Comparative Oncology Trials Consortium
DLBCL diffuse large B-cell lymphoma
ER estrogen receptor
FGF23 fibroblast growth factor 23
FISH fluorescence in situ hybridization
FSA fibrosarcoma
GBM glioblastoma multiforme
GEMM genetically engineered mouse model
GIST gastrointestinal stromal tumor
HS histiocytic sarcoma
HSA Hemangiosarcoma
IND investigational new drug
LD linkage disequilibrium
LSA lymphoma
MCT mast cell tumor
MRI magnetic resonance imaging
NCI National Cancer Institute
NHL non-Hodgkin's lymphoma
NIH National Institutes of Health
ODN oligodeoxynucleotides
ORR objective response rate
OS osteosarcoma
PD pharmacodynamic
PK pharmacokinetic
PR progesterone receptor
PTCL peripheral T-cell lymphoma
RMS rhabdomyosarcoma
SNP single nucleotide polymorphism
STS soft tissue sarcoma
TCC transitional cell carcinoma

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Glossary

Linkage disequilibrium The nonrandom association of alleles at different loci.
Kataegis Localized hypermutation in the somatic genome.