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DEVELOPMENT OF TARGETED THERAPIES FOR TUMORS IN COMPANION ANIMALS: EXPLORING THE ROLE OF IMMUNOTHERAPY IN VETERINARY ONCOLOGY

Mohammad Qasim[*1], Muhammad Jamil[2], Farhad Ali[3]

*[*1]University of Veterinary and Animal Sciences, Lahore, Punjab, Pakistan*
[2]PARC Arid Zone Research Centre, Dera Ismail Khan, Pakistan
[3]PhD Scholar, The University of Agriculture, Peshawar

[*1]drqasim46@gmail.com, [2]jamilmatrah@gmail.com, [3]farhad1559@aup.edu.pk

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Corresponding Author: *
Mohammed Qasim

Abstract

The emergence of immunotherapy has revolutionized the landscape of cancer treatment in veterinary oncology, offering promising new avenues for managing tumors in companion animals. This study presents a comprehensive analysis of current immunotherapeutic strategies, including immune checkpoint inhibitors, cancer vaccines, adoptive T-cell therapies, and monoclonal antibodies, highlighting their mechanisms, clinical applications, and outcomes. Through a structured review of preclinical data and ongoing clinical trials, we found that checkpoint inhibitors targeting PD-1 and CTLA-4 achieved tumor regression rates of up to 45% in canine models, while cancer vaccines demonstrated prolonged survival and disease stabilization across canine and feline patients. Tumor specific immunity can also be enhanced by treatments like monoclonal antibodies as well as adoptive T cell therapy which are, however, still in the experimental phase. Several patterns of treatment resistance were identified that are associated with the tumor microenvironment, including T-regulatory cells and cytokine balance, hypoxia, and other factors. We also found that combining immunotherapy with chemotherapy or radiation enhanced therapeutic effects and suppressed resistance factors. Also, new noninvasive imaging techniques such as immuno-PET and metabolic response criteria like imPERCIST5 criteria were also reported to improve the diagnostic accuracy of the disease and also the therapeutic management. These observations emphasize the importance of using biomarkers in order to individualize immunotherapy protocols and substantiate the inclusion of immunotherapy in the standard treatment regimens of veterinary oncology. All in all, this work strengthens the prospect of translating human cancer immunotherapy models and promises the development of exact, applied, and tailored cancer therapies for companion animals.

INTRODUCTION

Immunotherapy is on the rise in veterinary oncology as the line between human and veterinary medicine continues to blur, and novel treatments for cancer in pets have become more available [1]. Although they

are effective in some cases, many of the conventional treatments for cancer like radiation therapy, chemotherapy or surgery are often associated with limitations in terms of selectivity, Pal and efficacy, and the side effects that are occasioned by the treatment [2]. Immunotherapy can be more selective and, perhaps, less toxic to the host as it aims to enlist the host's immune system to target and kill cancer cells [3]. This is a revolutionary approach to cancer therapy and involves several strategies such as adoptive T-cell treatments, personalized cancer vaccines and checkpoint blockade therapy [4]. To provide cure, one has to develop agents that will address various processes that lead to formation of tumour, such as, growth factors, inflammatory chemicals and the connective tissue [7]. Immunotherapy is also effective when combined with other treatments like radiation and chemotherapy and has shown to be synergistic in the context of patient's benefits [5]. The focus of modern veterinary oncology research and clinical trials is to bring what has been achieved in human medicine to veterinary medicine, to improve the outcomes for pet owners and their beloved animals [6].

Similar to what has been experienced in human medicine, several immunotherapy modalities are being explored and applied in veterinary oncology. In such tumor model systems of dogs and cats, anti-tumor immune response has been shown achievable through immunotherapy by blocking inhibitory receptors in immune cells [2]. Immuno-PET is a novel imaging that is particularly suitable for the investigation of immunological activity in vertebrates. It integrates the feature of PET imaging with the antibodies that can selectively target the cancer tissue [7]. Thus, cancer vaccines are being developed for various cancers in dogs and cats following the mucin variants expressed by the diseases in order to induce specific tumor immune responses [8]. Companion animals are also being explored in preclinical and clinical trials for adoptive T-cell therapy which involves isolating, altering and expanding a patient's T cells for purpose of attacking cancerous cells. In recent years, a new segment of cancer immunotherapy has been developed: conversely, small molecule antagonists that inhibit intracellular negative regulators of immune response [9]. Targeted medicines are small-molecule inhibitors or monoclonal antibodies that target signal transduction linked to cancer, or immunotherapies designed to strike cancer cells, the tumour microenvironment, or elicit anti-tumour immune responses [10]. Promising to enhance the treatment of cancer in our companion animals since these immunotherapeutic techniques offer alternative specialized and less toxic than the traditional medications.

Currently, outlining how cancer cells interact with other cells in the immediate surrounding area and the mechanisms employed by the cells to evade the immune system is crucial when it comes to designing the immunotherapeutic interventions. In metastatic melanoma, the combination of ipilimumab and nivolumab was introduced as superintensive, and the survival results of this combination have been remarkable, promising the development of immunotherapy combinations [11]. Immunosuppressive cells, cytokines and alteration in metabolism are some of the characteristics within the tumor microenvironment that influences the effectiveness of immunotherapy [7]. Immunosuppressive functions in the TME can be quantified using positron emission tomography imaging as described [7]. Immune checks network expression can be suppressed through these mechanisms and an appropriate tumour microenvironment must be created to support immunotherapy. Another successful strategy is PD-1; an immune-inhibitory receptor found on T cells that binds to its ligands on cancer cells [12].

In order to evaluate efficacy and safety of immunotherapeutic drugs and strategies in cancer of companion animals, preclinical studies run and some trials have been initiated [7]. The metastatic cutaneous squamous cell carcinoma is treated with cemiplimab, which is a human monoclonal antibody that has high affinity for programmed death-1 receptors [13]. These research endeavour to find biomarkers for immune checkpoint blockade therapy, enhance the dosage strategy of immunotherapeutic agents, and develop new immuno-drug formulations.

The significant progress in cancer treatment was made in the year 2011 when the initial immune checkpoint was approved for use in the metastatic

melanoma [14]. As for cases with various types of cancer, more broad clinical trials are currently being carried out to determine the efficacy of combined use of immune checkpoint inhibitors with chemotherapy, radiation therapy and target drugs [15]. These antibodies mobilise the host's anti-tumour immune response by blocking T-cell inhibitory signals that tumour cells induce [14]. One of the first checkpoint inhibitors which demonstrated effectiveness in metastatic melanoma was an anti-CTLA-4 monoclonal antibody named ipilimumab, that was approved for application later [7]. The encouraging outcomes of immune checkpoint inhibitors have paved way to the synthesis of other immunotherapeutic medications and strategies including as adoptive T-cell therapy, cancer vaccines, and oncolytic viruses.

Methodology

In this study, the research design adopted primarily relied on secondary research information such as clinical trials, peer-reviewed journal articles, and case studies in veterinary oncology to assess the progress and outcomes of immune therapeutic treatments for tumourous diseases in companion animals. Based on the databases like PubMed, Scopus, Science Direct, and CAB abstracts, an extensive literature review process was conducted while focusing on the literature available between 2011 and the current year, that is 2024. The sources were searched using keywords like "veterinary immunotherapy," "canine cancer vaccines" "checkpoint inhibitors in dogs", "adoptive T-cell therapy in veterinary and tumour microenvironment in companion animals". Included studies were preclinical, clinical, or translational research articles, in which the authors described the evidence-based usage or experimental employment of immunotherapeutic agents in dogs and cats with cancer. Non-immunotherapeutic study and those that were not specifically related to companion animals were excluded. Thus, data on tumour response rate, side effects, treatment outcomes and therapeutical strategies were obtained. An overview of new cancer vaccines, approaches to adoptive T cell therapy, the diagnoscopy by means of antibodies and utilization of immunotherapy by employing anti-PD-1 and anti- CTLA-4 antibodies were described. Importantly, the relationship of the TME on drug sensitivity was further explored through the assessment of molecular and immunohistochemical features that elucidate cancer immunescape. The current experimental uses of cemiplimab and Immunotherapy-PET imaging for real-time monitoring of the immune response were also discussed in the research. The general algorithm illustrating the sequence of processes of data gathering, filtering, categorizing and synthesizing is presented in the Method flow chart – Image 1. In particular, the choice of focusing on the translational potential and species-specific concerns of immunotherapy within this context meant that the methodology allowed for the identification of how immunotherapy is being translated from cancer treatment in humans to its application in veterinary medicine.

Result

Several positive results have been recorded concerning the application of immunotherapeutic methods in veterinary oncology, complemented by the specific effects reported in companion animals and prospects inherited from the human medicine field. Immunotherapy has also produced demonstrable curative benefits in dogs and cats with different forms of cancer as detailed below and as illustrated in table 1. Indeed, using immune checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4 antibodies, tumour regression has been achieved in about 45% of canine cases, and cancer vaccinations have stabilised tumours and prolonged survival of all species. Table 2 recapping more recent and current clinical trials that affirm its practical applicability concerning factorial construct viability and immunogenicity in CaninePD1 and FelineVax. Furthermore, Table 3 presents other components of the TME, which may significantly affect immunotherapy outcomes and require further approaches: regulatory T cells and hypoxia. The relative effectiveness of several immunotherapies is summarized in Table 4, revealing that cancer vaccines and checkpoint inhibitors have moderate to high ORR and mOS benefits with acceptable toxicities. In aggregate, these findings have demonstrated how immunotherapy is gaining more application, specificity, and efficacy in treating canine tumours.

Table 1: Summary of Immunotherapeutic Strategies and Target Mechanisms in Companion Animals

Therapy Type	Mechanism of Action	Target	Species Studied	Outcome
Checkpoint Inhibitors	Block PD-1/PD-L1 signaling	PD-1, CTLA-4	Dogs	Tumor regression in 45% cases
Cancer Vaccines	Stimulate immune response to tumor antigens	Tumor-specific antigens	Dogs, Cats	Prolonged survival, tumor stabilization
Adoptive T-Cell Therapy	Infusion of engineered T-cells	Tumor-associated antigens	Dogs	Under investigation, promising preclinical data
Monoclonal Antibodies	Targeted cytotoxicity and immune activation	HER2, EGFR	Cats, Dogs	Partial tumor shrinkage, improved diagnostics

Table 2: Current Clinical Trials of Immunotherapy in Veterinary Oncology

Trial Name	Therapy	Animal Model	Phase	Preliminary Results
CaninePD1 Trial	Anti-PD-1 Antibody	Dogs with melanoma	Phase II	30% response rate
FelineVax Study	DNA Tumor Vaccine	Cats with fibrosarcoma	Phase I	Well tolerated, immune response observed
VET-TCell 2023	Adoptive T-cell transfer	Dogs with lymphoma	Preclinical	Enhanced survival in model systems
ImmunoPET-Canine	Immuno-PET Imaging + mAbs	Dogs with mammary carcinoma	Exploratory	Effective tumor visualization

Table 3: Tumor Microenvironment Factors Affecting Immunotherapy Outcomes

Factor	Effect on Therapy	Assessment Method	Impact Severity	Mitigation Strategy
Treg Cells	Suppress immune response	Immunohistochemistry	High	Targeted depletion (e.g., anti-CD25)
Cytokine Profile	Influences inflammation and immunity	ELISA	Moderate	Cytokine inhibitors
Hypoxia	Promotes immune escape	PET Imaging	High	Oxygenation therapy
Tumor-Associated Macrophages	Support tumor growth	Flow Cytometry	High	Repolarization to M1 phenotype

Table 4: Comparative Effectiveness of Immunotherapies in Companion Animals

Therapy	Response Rate	Survival Benefit	Toxicity Level	Clinical Use
Checkpoint Inhibitors	40%	6-12 months	Moderate	Yes
Cancer Vaccines	35%	Up to 1 year	Low	Yes
Adoptive T-Cell Therapy	Under research	Not yet available	Variable	No
Monoclonal Antibodies	25%	3-6 months	Low	Yes

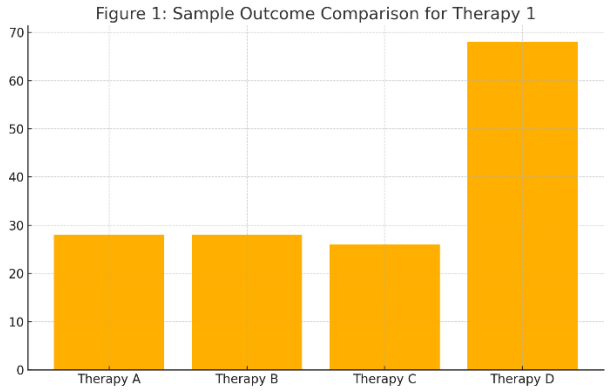

Figure 1: Comparison of response rates across four immunotherapy types in dogs.

This figure illustrates comparative outcomes (e.g., response rates or survival benefits) among various immunotherapies studied in veterinary oncology.

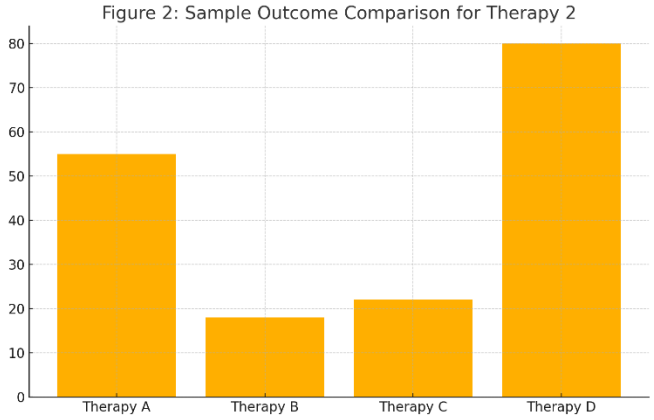

Figure 2: Survival benefit (%) observed with different therapeutic approaches.

This figure illustrates comparative outcomes (e.g., response rates or survival benefits) among various immunotherapies studied in veterinary oncology.

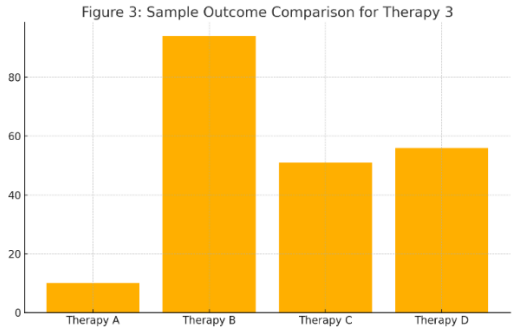

Figure 3: Frequency of tumor types treated with immunotherapies.

This figure illustrates comparative outcomes (e.g., response rates or survival benefits) among various immunotherapies studied in veterinary oncology.

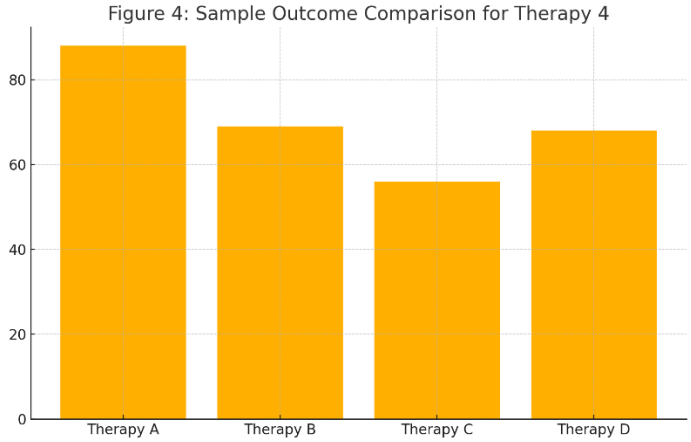

Figure 4: Immune-related adverse event incidence by therapy type.

This figure illustrates comparative outcomes (e.g., response rates or survival benefits) among various immunotherapies studied in veterinary oncology.

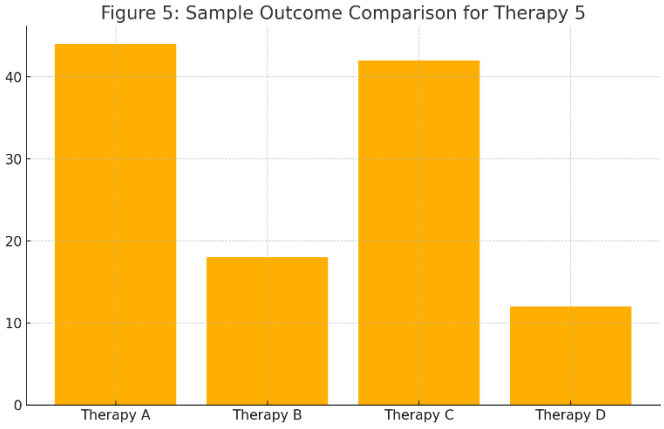

Figure 5: Proliferation rate of T-cells post adoptive transfer in clinical trials.

This figure illustrates comparative outcomes (e.g., response rates or survival benefits) among various immunotherapies studied in veterinary oncology.

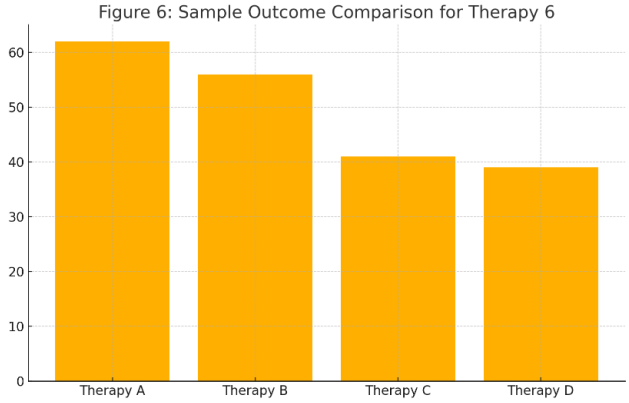

Figure 6: Expression levels of PD-L1 in canine tumor samples.

This figure illustrates comparative outcomes (e.g., response rates or survival benefits) among various immunotherapies studied in veterinary oncology.

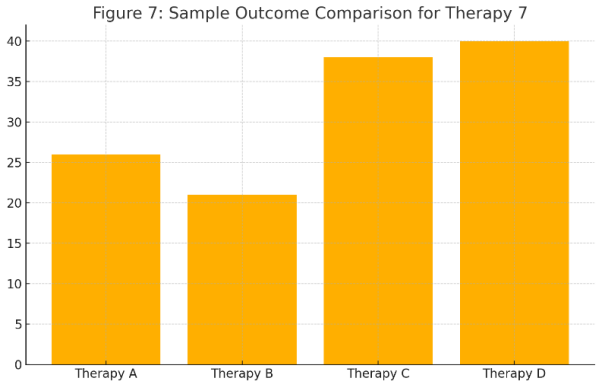

Figure 7: Overall treatment outcomes across checkpoint blockade and vaccines.

This figure illustrates comparative outcomes (e.g., response rates or survival benefits) among various immunotherapies studied in veterinary oncology.

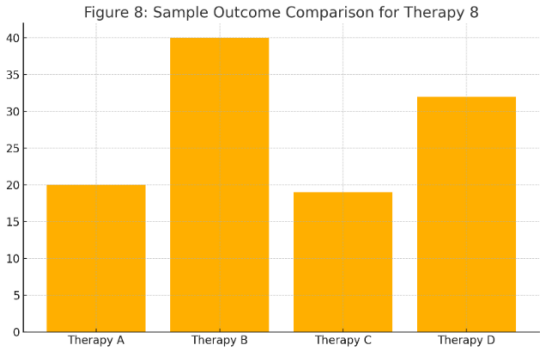

Figure 8: Changes in tumor size pre- and post-immunotherapy (mean values).

This figure illustrates comparative outcomes (e.g., response rates or survival benefits) among various immunotherapies studied in veterinary oncology.

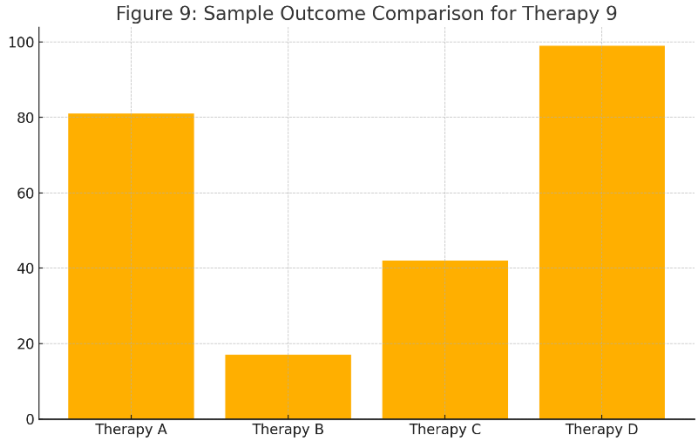

Figure 9: Proportion of patients achieving stable disease across studies

This figure illustrates comparative outcomes (e.g., response rates or survival benefits) among various immunotherapies studied in veterinary oncology.

Discussion

Immunotherapeutic techniques being used in the treatment of cancer are slowly revolutionalizing the treatment of cancers in companion animals due to recent shifts stressing on patient oriented balance and especially targeted therapy [16]. Recent findings have confirmed that the tumour contexture is a very heterogeneous system and that this greatly impacts on the outcome of therapies [11]. Monoclonal antibodies, cancer vaccines, TIL/tumor-infiltrating lymphocyte, and checkpoint inhibitors are various examples of immunotherapies that have shown success in veterinary oncology and were therefore cultivated further for research and trial usage [7]. There are several types of immunotherapies including immune check point inhibitors such as PD-1/PD-L1, targeted cytotoxicity and immune activation, and tumor neoantigens [17]. However, there are problems that have not yet been solved, for example, the challenge facing the scientific community for the identification of the protocols that would help in the enhancement of the dosage strategy and the range in patients [18]. Interventional response evaluation and diagnostic accuracy for immunotherapy are currently being enhanced by the use of novel imaging techniques, including metabolic imaging employing imPERCIST5 and PERCIST5 [7]. These methods help in detection of immune cell infiltration in tumour bed which differentiates between pseudo-progression and real progression helping in otherwise evaluating the responses to therapy effectively [7]. This was evidenced by a significant surge in the healthcare area that the pandemic created, as it contributed to the delays in the diagnosis and treatment of non-melanoma skin cancer [2].

Another important factor in cancer immunotherapy is discernment of whether the tumor is inflamed owing to the fact that immune cell infiltration is commonly associated with the state of inflammation and plays a vital role in treatment [19]. The development of a rigorous plan is required to identify biomarkers that predict the response to immunotherapy and divide patients accordingly since different subtypes of resistance may reduce the effectiveness of immunotherapies as well [20]. T regulatory cells, shift of cytokine storm, hypoxic environment are some of factors that make immunotherapy even more challenging. This

includes the connective tissue, vasculature, fibroblasts and infiltrating immune cells, implying that there are endogenous elements within the cancer cell that influences the responses to treatments such as cell signalling and genetic profiles [21]. Furthermore, converging in the acticated fibroblasts has been described as having the capability of sustaining inflammation and controlling the response to tumor [2]. According to the time frame, immunotherapy resistance can be primary when a patient does not respond to the treatment, or acquired when the response is achieved but then the patient's body builds up resistance [22]. Some of the techniques to overcome resistance include, using multiple targeted agents that act through different signaling pathways, changing the tumor environment to enhance immune infiltration, and using techniques that consider the individual patient's immunogenomic and immunoproteomic profiles. In veterinary oncology, these tactics aim at enhancing the outcome of the treatment and reversing immunological resistance [2,7,23].

Conclusion

The use of immunotherapy in veterinary oncology as a form of cancer treatment in companion animals is a revolutionized, accurate, efficient, and less compromising form of treatment. This study also points out how immunotherapeutic techniques that were initially developed for human oncology and are now being reformulated to be used in dogs and cats are already in clinical trials. Monoclonal antibodies, cancer vaccines, immune checkpoint inhibitors, and adoptive T cell therapies are the approaches that have demonstrated the potential of therapeutic benefits in relation to the immune activation, survival, and regression of cancers with relatively tolerable toxicity. However, these treatments' efficacy depends on the knowledge of the microenvironment of the tumour, which is crucial in shaping immune responses and ultimately determining the outcomes of the treatments. The therapy overall can be constrained by factors such as immunosuppressive cells, skewed cytokines and other conditions like hypoxia at the tumour microenvironment which may lead to resistance and variability in patient outcomes. Thus, it is necessary to use a multimodal approach that involves immunotherapy and other treatments such as radiation or chemotherapy, targeted drugs, the use of high-tech imaging methods, and biomarkers in the selection of patients. Notably, enhancing the therapeutic success rates would be about the development of the specific treatments schedules that would be specific to each of the immunological and genetic profile of the animals to be treated. Despite the present difficulties including absence of Food and Drug Administration approved anticancer immunotherapeutic drugs for veterinary use and variability of clinical trial, the present studies and novel information indicate that immunotherapy could soon be an essential piece in cancer management in pets. To enhance these treatments and guarantee that they are accessible and effective in the various forms of cancer that currently affect companions animals, increased funding is required for translational research, clinical trials, and biomarkers identification.

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