Introduction

Clinical trials in oncology represent a critical link between basic science research and clinical practice. Because standard chemotherapy has usually limited efficacy against most cancers, there has been an effort over recent decades to develop targeted agents and cancer vaccines that have led to significant improvement in outcomes for various cancers in humans (Zhang et al., 2009; Raval et al., 2014). Likewise, efforts have been pursued in veterinary oncology, and novel promising cancer therapeutics consisting of targeted agents (Hahn et al., 2008; London et al., 2009) and cancer vaccines (Bergman, 2010; Denies and Sanders, 2012) represent some of the most exciting opportunities in veterinary oncology.

Targeted therapy is used to describe agents that affect neoplastic cells and usually spare normal cells by interfering with specific molecules required for tumour development and growth (the so-called therapeutic targets). In humans, targeted agents include monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs), and these are already major treatment options for cancer together with cytotoxic chemotherapeutic agents (Imai and Takaoka, 2006). The advantage of these drugs is the improved efficacy and selectivity they offer by blocking specific mechanisms involved in malignant transformation and progression. Validated therapeutic targets include membrane receptors playing a direct role in cancer biology, components of cytoplasmic signalling pathways, cell cycle regulator proteins, circulating growth factors, and proteins or factors involved in angiogenesis (Traxler, 2003).

Approved veterinary targeted drugs include toceranib and masitinib, which target, among others, the KIT receptor (Hahn et al., 2008; London et al., 2009). Both exhibit high response rates as single agents in canine mast cell tumours with the targeted KIT mutation (Bonkobaara, 2015). Particularly, toceranib yielded higher response rates in dogs with mutated vs. wild-type c-KIT (69% and 37%, respectively) (London et al., 2009). Masitinib significantly prolonged survival in dogs with mutated vs. wild-type c-KIT (417 and 182 days, respectively) (Hahn et al., 2008).

In contrast to TKIs, mAbs generally have a higher specificity for their targets, a longer half-life (allowing for monthly administrations), and can be optimised using recombinant and protein technologies to improve their properties (Douthwaite and Jermutus, 2006). Several mAbs are approved for human use and an increasing number are currently in development, further highlighting the success of this approach. To reduce the risk of adverse immune responses, humanised mAbs and even fully human antibodies are currently the preferred approach. Antibody–drug conjugates (ADCs) offer a potentially new way to treat cancer in people by combining the unique targeting of mAbs with the cancer-killing ability of cytotoxic drugs, thereby allowing for sensitive discrimination between healthy and diseased tissues (Bidard and Trédan, 2014).

While passive immunotherapy holds significant potential for treating cancer, therapeutic mAbs have not yet been introduced in veterinary oncology. Several tumour-associated antigens, including CD20 (Jubala et al., 2005), epidermal growth factor receptor (EGFR) (Gama et al., 2009; Fukuoka et al., 2011; Sabattini et al., 2015), HER-2 (Ferreira et al., 2010; Singer et al., 2012), vascular endothelial...
growth factor (VEGF) (Aresu et al., 2014) or platelet-derived growth factor receptor (PDGFR) (Maniscalco et al., 2013), have been identified in canine malignancies; however, mainly for financial reasons, only a few attempts have been made to generate ‘caninised’ mAbs (Jeglum, 1996; Singer et al., 2014) or to evaluate humanised mAbs in veterinary oncology (Impellizzeri et al., 2006).

In the 1980s, the United States Food and Drug Administration (FDA) approved the first chimeric antibody, rituximab, for the treatment of human B-cell non-Hodgkin lymphoma (Grillo-López, 2000). Rituximab represents one of the best examples for mAbs of proof-of-concept. Unfortunately, it failed to show efficacy in canine B-cell lymphoma due to the lack of homology between humans and dogs of-concept. Unfortunately, it failed to show efficacy in canine B-cell lymphoma due to the lack of homology between humans and dogs in the CD20 epitope that is recognised by rituximab (Impellizzeri et al., 2006; Ito et al., 2014). In general, lack of epitope homology between human and canine proteins and consequently cross-reactivity of the mAbs for the canine protein limit their use in dogs.

In humans, many vaccines have reached Phase 2–3 clinical trials. Most paired tumour-associated antigens (TAAs) have an immune-activating adjuvant to stimulate the humoral and/or cellular immune responses against these TAAs (Schlom, 2012). In veterinary oncology, a variety of vaccines eliciting an anti-tumour immune response have been generated, involving peptides, cells, DNA, viruses and ex vivo generated dendritic cells (Bergman et al., 2003; Turek et al., 2007; Peruzzi et al., 2010; Grosenbaugh et al., 2011; Sorenmo et al., 2011; Marconato et al., 2014; Riccardo et al., 2014).

Targeted therapy and cancer vaccines have introduced new challenges for oncologists, such as determining the optimal dosing and administration schedules, and a proper understanding of the mechanism of activity of these experimental agents has become essential for the optimal design of any clinical study. In clinical trials evaluating traditional chemotherapeutic agents, toxicity is generally determined through the degree of myelosuppression and gastrointestinal (GI) side effects. Most conventional chemotherapeutic cytotoxic agents cause cell death by directly inhibiting DNA synthesis or by interfering with DNA function. For these reasons, chemotherapeutic cytotoxic agents are not tumour-specific and are thus associated with considerable morbidity. Conversely, targeted therapy and cancer vaccines usually do not cause significant toxicity. In addition, assessment of efficacy may require a paradigm shift. Effective cytotoxic chemotherapy leads to tumour volume reduction, while some targeted therapies may impart a clinical benefit by stabilising tumours rather than by shrinking them. For cancer vaccines, efficacy may be even harder to anticipate.

These new antitumour strategies challenge the existing paradigm for experimental design, conduct and analysis of Phase 1, 2 and 3 oncology clinical trials, prompting oncologists to turn to different endpoints for appropriate dosing, schedule selection, and efficacy assessment (Park et al., 2004).

In this review, the impact of targeted therapies and cancer vaccines on the design of oncology clinical trials is discussed in terms of target identification, study endpoints, and overall clinical protocol.

Target identification

Identifying the biological origin of disease and the potential targets for therapeutic intervention is the first step in target-based drug discovery. A target-based drug discovery programme is aimed at developing drugs that selectively modulate the effects of selected genes or gene products (the therapeutic targets) without adversely affecting other vital molecular mechanisms. This involves discovering these targets, a process referred to as target identification.

Signal transduction pathways involved in cancer biology are generally investigated using sequencing techniques. For some human tumours, gene expression profiles have been proposed as potential biomarkers to predict treatment response and to identify new therapeutic targets. Human tumours may have distinct molecular subtypes and different therapeutic approaches may be required for each subtype (Boede et al., 1996). Only recently, genomic technologies have been considered for canine tumours, and in the future these data will be validated and used for specific targeted therapy (Klopfleisch, 2015).

Different approaches may be considered for target identification. One approach is to compare the amounts of individual proteins in cancer cells with those expressed in normal cells. Proteins that (1) are over-expressed in cancer cells, (2) provide a selective advantage to tumour cells (growth or survival), and (3) are not being expressed (or expressed at much lower levels) by non-cancerous cells represent ideal targets (Zhang et al., 2009). Another approach is to determine whether neoplastic cells produce mutated proteins that participate in cancer generation and progression. Chromosomal abnormalities may also be present in neoplastic cells, resulting in fusion genes whose products may drive cancer development. Such fusion proteins may become potential targets for treatment (Cavallo et al., 2007; Iezzi et al., 2012; Aricò et al., 2014).

Even if a good therapeutic target is identified and an inhibitor of that target with in vitro or in vivo pharmacological efficacy is available, response in the clinic cannot be fully anticipated, as effectiveness of targeted therapy does not always correlate with target overexpression (Douthwaite and Jermuth, 2006). Thus, some target-positive tumours may fail to respond (primary resistance), while some target-negative tumours may show some response. It is possible that blocking the growth factor receptors may benefit certain patients even if the cancer is not overexpressing them, thereby challenging clinical trial design, particularly patient eligibility (Nicolaides et al., 2014).

Selection of primary endpoints

In human oncology patients, overall survival (OS, i.e. the interval from randomisation to death from any cause) represents the gold standard endpoint for ascertaining the clinical benefit of (and approving) traditional anticancer treatments, as it is not subject to investigator interpretation (Williams et al., 2004). Possible challenges include crossover or subsequent therapies (which may confound the survival benefit that can be attributed to any individual drug or protocol) and the requirement for a large population and/or a long follow-up compared to other endpoints in order to show statistical differences, especially for slowly progressing cancers (Johnson et al., 2003). In veterinary oncology, OS is not the most appropriate endpoint, as it may be biased by several tumour-unrelated factors, including the owner’s financial concerns.

Time-to-progression (TTP, i.e. the interval from randomisation to disease progression) represents another commonly used endpoint. Patients must be evaluated on a regular basis, and all disease sites should always be assessed. In addition, the same assessment technique should be used at each follow-up to reduce bias (Johnson et al., 2003). This clinical trial endpoint can be achieved sooner than OS and there is no confounding effect by crossover or use of second-line therapies. Nevertheless, TTP is at best only an estimate, as it may vary based on the scheduled frequency of evaluation.

Objective response rate (ORR) is also commonly used and refers to the portion of patients showing a predefined tumour size reduction (depending on the adopted response criteria, WHO [World Health Organization] vs. RECIST [Response Evaluation Criteria in Solid Tumours]) (Nguyen et al., 2013; Heller, 2015) for a minimum time period (typically 21–28 days). Response duration is measured from the initial response until documented tumour progression (Johnson et al., 2003). Like TTP, response duration can only be estimated and varies based on the frequency of assessment.

TTP and ORR may be considered ideal primary endpoints, but both can differ to measure in veterinary oncology, because of
costs, need for advanced imaging technology and anaesthesia for many staging tests, and owner compliance. In addition, a statistically significant difference in TTP or ORR between treatment arms may not necessarily translate into a clinical benefit. Furthermore, possible clinical benefits associated with tumour shrinkage may not necessarily justify the toxicity typically associated with cytotoxic drugs (Williams et al., 2004).

For targeted drugs, which are often cytostatic rather than cytotoxic, endpoints other than OS and ORR are needed. Cytostatic agents may impart a clinical benefit by slowing or stopping tumour growth without any shrinkage (Korn et al., 2001). Typical objectives are disease stabilisation and delayed tumour response, but also tumour swelling followed by regression. If WHO or RECIST criteria are used, such responses are ignored, and late responders may be erroneously classified as non-responders.

Similarly, active immunotherapy may yield responses that are not captured by the WHO or RECIST criteria. Vaccines first activate the immune system and then build up an immune response, possibly leading to disease stabilisation and survival improvement (Hoos, 2012). As with targeted agents, tumour infiltration by inflammatory cells, which is typically observed following immunotherapy, may first lead to an increased tumour diameter. According to the WHO or RECIST criteria, this would be classified as progressive disease, possibly leading to a premature trial discontinuation, and missing a late biological effect induced by immunotherapy.

Based on the unique patterns of clinical response that are obtained by targeted or immune-modulating therapies, alternative endpoints are necessary (Bilusic and Gulley, 2012). In particular, based on the assumption that many of these new agents are expected to work only in narrowly defined patients, patients need to be prospectively identified and pre-screened for biomarkers, and the development of the drug needs to be linked to the development of a molecular diagnostic product (a companion diagnostic). Thus, surrogate markers of efficacy and benefit need to be defined and validated and will be specific to both the agent being evaluated and the tumour being treated.

It is certainly appropriate to consider biological endpoints and surrogate markers in clinical trials that reflect the proposed mechanism of action of the agent under investigation (Korn et al., 2001), including T-cell activation and T-cell memory markers for immunotherapeutic agents, or gene status and protein expression for targeted agents. This requires knowledge of the target to be measured, a specific and reproducible assay for target inhibition (i.e. evidence of target engagement and of a pharmacodynamic [PD] effect), knowledge of target distribution in the tissues of interest, and accessibility to the appropriate tissue (Korn et al., 2001). Importantly, imaging studies for tumour response evaluation should be obtained after an appropriate time has elapsed for a response to be initiated. Sequential restaging with enough time after therapy to gauge response will also provide the necessary time for complex pathways intrinsic to immunotherapy or targeted agents to engage. However, it should be acknowledged that, due to the intrinsic difficulties in identifying and validating good surrogate markers, biomarker endpoints are mainly examined in an exploratory mode.

**Clinical trial design for immunotherapy and targeted agents**

With traditional cytotoxic chemotherapy, there are well-established experimental designs for Phase 1, 2 and 3 clinical trials (Vail, 2007). These are based on the paradigm that with increased haematological toxicity, cancer cells are more likely to be killed, thereby leading to tumour shrinkage and clinical benefit. It is also assumed that there is an increased dose–response and dose–toxicity relationship. To avoid treating patients with ineffective therapies, the three phases are sequential, and the decision to treat additional patients depends on the safety and efficacy observed in patients from the previous cohorts.

Targeted therapies are not necessarily expected to shrink tumours; rather they most often inhibit growth and/or prevent metastasis. Consequently, the traditional designs for Phase 1, 2 and 3 clinical trials may not be adequate (Beeram and Patnaik, 2002). Efficacy trials may therefore need to incorporate measures of antineoplastic behaviour other than changes in tumour size. These main differences are summarised in Table 1.

**Phase 1 (dose-finding) clinical trials**

In Phase 1 trials with cytotoxic drugs, acute dose-limiting toxicities are the primary endpoint. A standard dose-escalation with cohorts composed of a fixed number of patients treated at each of sequential dose levels is used to determine the maximal tolerated dose (MTD) to be used in the subsequent Phase 2 and Phase 3 clinical trials (Skipper, 1964). It is commonly thought that more is better, based on the assumption that both efficacy and toxicity increase monotonically with dose: theoretically, higher tumour concentration translates into decreased neoplastic cell resistance and greater clinical activity (Le Tourneau et al., 2009).

Conversely, targeted drugs may lack clinically significant organ toxicity, since they modulate specific aberrant pathways in cancer cells while sparing normal tissues (Korn et al., 2001). Thus, their toxicity and efficacy may not be dose-dependent (Cannistra, 2008). It remains undetermined whether there is a clear and monotonic dose-response/dose–toxicity relationship with targeted therapies, as targeted drugs usually have maximal target inhibition at non-toxic doses. This challenges the principle that more is better. Consequently, increasing the dose to toxicity levels may not be relevant, making MTD as a surrogate endpoint for activity inappropriate. Conversely, demonstrating that targeted drugs have the desired effect is the most important aspect of early clinical development.

As an alternative to MTD, the optimal biological dose (OBD) has been proposed (Korn, 2004). Ideally, the OBD is based on escalating the dose to reach a predefined pharmacological parameter, i.e. the target is saturated with the drug or the target-mediated pathway is optimally altered. Therefore, before initiating a Phase 1 with targeted drugs, it is important to know that: (1) the test article can reach or engage the target (target engagement); (2) the target is modulated by the experimental drug; (3) the tumour is altered by modulating the target activity, and (4) higher doses will not improve outcome further (Parulekar and Eisenhauer, 2004; LoRusso et al., 2010). Although these concepts seem logical, the measurement of an effect on a molecular target is associated with several challenges, including defining the appropriate measure for target effect, restricting patient enrolment to those with tumours expressing the target, and collecting serial tumour samples. Pharmacokinetic (PK) endpoints, such as achieving targeted plasma levels of the drug, may help with Phase 1 study dose selection if sufficient preclinical data exist demonstrating a convincing PK–PD relationship. Veterinary oncologists do face further challenges, including the fact that trials are typically only partially funded and that population sizes are typically small. The latter aspect is partly attributable to the reluctance of owners to treat their pets with drugs that may not be effective or may cause significant toxicity. Thus, to utilise limited clinical resources rationally and to accelerate patient accrual, the model of large multi-institutional studies is being pursued. Although accrual time and population size may improve, keeping all sites informed on a real-time basis about safety issues represents a non-negligible challenge.

Determining the OBD of targeted agents when these agents are incorporated into standard chemotherapy regimens brings another level of complexity (Mitchell et al., 2012; Robat et al., 2012; Pan et al., 2014). Since targeted and chemotherapeutic drugs have different mechanisms of action and non-overlapping toxicities, the
Table 1

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<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tr>
<td><strong>Objective</strong></td>
<td>Cytotoxic Activity</td>
<td>Cytotoxic Activity</td>
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<tr>
<td>MTD, PK</td>
<td>Immunogenicity, biological activity, clinical activity</td>
<td>Disease-specific efficacy</td>
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<tr>
<td>OBD, PK, toxicity</td>
<td>Disease-specific activity</td>
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<td>All histotypes</td>
<td>Target-bearing tumours</td>
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<td>Dose-escalation</td>
<td>Fixed dose</td>
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<td>Toxicity</td>
<td>Time to progression</td>
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<td>Guided</td>
<td>Controlled</td>
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<td>Inhibition of target activity</td>
<td>Biological activity</td>
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<td>PK, pharmacokinetics; MTD, optimal biological dose</td>
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Recommended dose for Phase 2 trials for the drug combination is usually expected to be near the recommended dose of each drug given as single agents (Paller et al., 2014). Nevertheless, it remains challenging to determine if and which drugs should be administered at full dose and how to proceed with dose escalation.

There is a lack of standardised clinical trial designs for the development of cancer vaccines. The major challenges with these agents include the difficulty to assess clinical responses due to delayed responses, the lack of valid biomarkers for efficacy, the lack of correlation between the MTD and the maximal effective dose, the absence of MTD for many immunotherapeutic agents, and potentially the criteria for patient selection (Horng and Pullman, 2004; Lesterhuis et al., 2011). An insufficient understanding of the underlying mechanism of action may also hamper the development of clinically useful assays to monitor immune responses, thus hampering the selection of the optimal dose, schedule and administration route.

The Phase 1 concept of dose escalation to find an MTD or to characterise the PK properties does not apply with most cancer vaccines (Simon et al., 2001). Vaccines are generally much safer than conventional chemotherapeutic agents and the dose yielding sufficient immunogenicity and biological activity is unlikely to cause significant toxicity (Simon et al., 2001). Based on this, initial clinical trials involve the administration of a fixed dose of vaccine. The goal is similar to those of most Phase 2 trials: it is not based on safety, but rather on determining whether the vaccine shows sufficient biological activity to warrant further investigation (Mackiewicz and Mackiewicz, 2009). In contrast to systemic drugs that are absorbed, metabolised and excreted, cancer vaccines are usually injected intradermally, subcutaneously or via electro-gene transfer after intramuscular injection, thus challenging the development of a meaningful PK assay. Phase 1 cancer vaccine trials should establish an active dose regimen associated with biological (immune response) or clinical activity, thereby allowing the design of randomised efficacy trials in the target population.

Another striking difference involves patient enrolment. Conventional chemotherapy Phase 1 trials enrol patients with various tumour types at a late stage with one secondary objective being the identification of a specific tumour type responding to the drug. Vaccines are instead tumour-specific. Therefore, the selection of the appropriate population is of utmost importance (Mackiewicz and Mackiewicz, 2009).

**Phase 2 (activity) clinical trials**

In Phase 2 trials, cytotoxic chemotherapeutic drugs administered at the optimal dose and schedule obtained from Phase 1 studies are evaluated for preliminary evidence of efficacy, with ORR typically used as a primary endpoint. Complete or partial response is generally measured as tumour shrinkage. Phase 2 trials are either uncontrolled or comparisons are made with historical controls. These trials are restricted to patients with specific histotypes, selected based on the activity of the test agents in preclinical models, mechanism of action, and preliminary activity observed in Phase 1 trials.

Phase 2 trials represent the biggest challenge for targeted therapy. Firstly, many targeted drugs do not induce complete or partial responses, as they typically arrest tumour growth. Consequently, it seems reasonable to include ‘stable disease’ in the ORR as a primary endpoint (Eisenhauer, 1998). With this expanded endpoint, the traditional Phase 2 design can still be used, provided that reliable historical data are available for which similar procedures were used to assess response and progression. Alternatively, concurrent controls are required.

Secondly, the population most likely to benefit from targeted therapy is generally unknown as the clinical effect is directly related to the level of target inhibition. Traditional Phase 2 studies ignore the clinical and molecular heterogeneity of various cancers arising...
in a single organ and similarities between cancers from different organ sites, tending to differentiate patients by the tissue of origin (Simon and Maitournam, 2004). In Phase 2 trials, definition of the population most likely to respond is critical.

Possible additional endpoints include changes in tumour biomarkers, measures of target inhibition, advanced diagnostic scanning or TTP (Eisenhauer, 1998). While these endpoints are promising, many challenges remain, including practical issues such as feasibility, accuracy issues such as frequency and methodology of restaging, and validation issues such as measurement of target inhibition/clinical outcome. The latter poses a serious challenge, as the acquisition of pre- and post-treatment tumour biopsies makes this approach difficult (Eskens and Verweij, 2000).

Based on this, randomised discontinuation Phase 2 trials may be better to guide decisions on cytostatic agents in contrast to standard Phase 2 designs (Rosner et al., 2002), with the major advantage being the ability to select the subpopulation mostly benefitting from the drug. In a discontinuation design, all patients receive the investigational targeted drug. Treatment is continued if an objective response is obtained or in case of clinical benefit; otherwise, treatment is stopped. In case of stable disease, patients are randomised in a placebo-controlled double-blind manner to continue or discontinue therapy (Freidlin and Simon, 2005). The primary endpoint is the percentage of patients in each randomised group maintaining stable disease at an arbitrary post-randomisation time point (Freidlin and Simon, 2005).

With regard to vaccines, conventional Phase 2 trials are generally replaced by ‘efficacy trials’, which are intended to be a direct follow-up to proof-of-principle trials. Their design can be either like conventional Phase 3 trials or randomised Phase 3 trials with prospectively defined efficacy criteria (Hoos et al., 2007).

Given the unlikely possibility of overcoming a large tumour burden with immunotherapy alone, this modality is best suited for the adjuvant setting, following eradication of the primary tumour by surgery or multimodal therapy. Vaccines may therefore target minimal residual disease (MRD) and generate immunity to protect from relapse. On the whole, patients without clinical evidence of disease may have more intact immune systems and be more appropriate candidates for tumour vaccines than patients with more advanced measurable or metastatic disease.

Clinical endpoints (including tumour shrinkage, reduction in biomarker levels or delay in TTP or tumour stabilisation) and/or immunological endpoints are commonly used for efficacy tumour vaccine studies (Simon et al., 2001). Tumour shrinkage is considered appropriate only if the target patients of Phase 3 studies are those with bulky disease. If TTP is measured, the study design needs to be randomised with a no-vaccine control group (Simon et al., 2001). With immunological endpoints, Phase 2 studies require the definition of the immunological response at the outset and reproducibility on repeated specimen sampling from the same patient. Unless the mechanism of immunological action is well understood, assay variability and uncertainty related to clinical relevance may make immunological endpoints problematic (Hoos et al., 2007).

Phase 3 (efficacy) clinical trials

Phase 3 clinical trials are the most critical for regulatory approval. In Phase 3 trials, cytotoxic chemotherapy drugs are evaluated for definitive evidence of efficacy. The classic Phase 3 study is a randomised controlled design with time-to-death due to all causes as primary endpoint aimed at comparing new regimens with standard therapy. For targeted drugs, the design remains relatively unchanged. Common Phase 3 trial designs include the randomise-all design, targeted design, and strategy design (Hoering et al., 2008). In the randomise-all design, the target status of the patient is assessed and all patients are randomised to one of two treatments, regardless of the status. This trial addresses the question of whether or not the new drug is beneficial for all patients, with the possibility of identifying subgroups of responders (target-positive). If the mechanism of the test agent is well understood, then the best design is the targeted design, whereby patients are first tested for the marker and, only if positive, enrolled in the trial and randomised to the two treatment arms (Simon and Maitournam, 2004). Such a targeted design tests whether or not the drug works for a specific subset of patients (target-positive).

The strategy design tests whether target-based treatment is superior to standard therapy, regardless of the target status. Patients are randomised between target-based treatment (target-positive patients receiving the new drug, target-negative patients receiving standard of care) and every patient, regardless of their marker status, receiving standard of care (Hoering et al., 2008).

Principles for Phase 3 trials apply equally for vaccines, including the need for a randomised control group and selection of an endpoint reflecting a clinical benefit. Phase 2 and 3 trials for cancer vaccines are part of the efficacy trials.

Conclusions

While the pharmaceutical industry is developing more targeted drugs for cancer treatment in humans, there are very few targeted drugs available for veterinary oncology. In the future, companion animals could become a useful translational research tool to facilitate innovation in veterinary and human oncology, especially for those new therapeutic approaches that challenge the current traditional clinical trial designs.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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