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REVIEW ARTICLE

Immunogenic Cell Death in Canine Lung Cancer: A Comparative Veterinary Oncology (Review of Animal Models and Human NSCLC)

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ABSTRACT

Primary canine lung carcinoma is uncommon but clinically aggressive and may provide a spontaneous, immunocompetent model for human non-small cell lung cancer (NSCLC). This review evaluated evidence that targeted therapies induce immunogenic cell death (ICD) across human, canine, and murine lung cancer models and examined conserved tumor-microenvironment barriers to ICD-driven immunity. PubMed, Scopus, and Web of Science were searched for peer-reviewed studies published from January 2000 to June 2026 that assessed canonical ICD hallmarks—calreticulin exposure, ATP release, HMGB1 release, or type I interferon signaling—after targeted therapy. Eligible studies were synthesized narratively and comparatively. Seventy-five studies were synthesized. Results are organized into five thematic areas: (1) canine lung carcinoma as a spontaneous veterinary disease model, (2) veterinary and companion-animal evidence relevant to ICD, (3) human NSCLC evidence as a comparative reference, (4) conserved immune and stromal barriers across species and (5) animal-model evidence informing future veterinary trials. The synthesis reveals that while the molecular machinery for ICD induction and sensing is highly conserved, the tumor microenvironment—dominated by macrophage-mediated efferocytosis—constitutes the critical rate-limiting checkpoint for translating ICD into anti-tumor immunity across all species examined. Available evidence supports cross-species conservation of major ICD pathways and suggests that canine lung cancer may be useful for investigating mechanisms that limit ICD-driven immunity. Nevertheless, the reproducibility, clinical relevance, and therapeutic benefit of combining ICD-inducing agents with microenvironment-targeted treatments in dogs remain uncertain and require validation in larger, controlled prospective studies.

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INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality in both humans and companion dogs (Fleming *et al*., 2011; Sung *et al*., 2021). In human oncology, the recognition that certain chemotherapies and molecularly targeted agents induce immunogenic cell death (ICD) has fundamentally reframed their mechanism of action, positing that long-term therapeutic success depends on the activation of adaptive anti-tumor immunity (Kroemer *et al*., 2013; Galluzzi *et al*., 2017). ICD is a regulated form of cell death defined by the spatiotemporally coordinated emission of damage-associated molecular patterns (DAMPs): surface-exposed calreticulin (ecto-CRT), secreted ATP, passively released high mobility group box 1 (HMGB1), and a type I interferon (IFN) transcriptional response. These signals collectively license dendritic cells (DCs) to cross-present tumor antigens and prime CD8+ T cell responses (Krysko *et al*., 2012; Kroemer *et al*., 2013).

Concurrently, the field of comparative oncology has matured, with spontaneously arising canine lung adenocarcinomas recognized as a powerful model that faithfully recapitulates the genetic, microenvironmental, and immunological complexity of human NSCLC (Paoloni and Khanna, 2008; Rowell *et al*., 2011). Canine

pulmonary adenocarcinomas harbor targetable molecular alterations, particularly involving HER2/ERBB2, with emerging evidence for additional actionable pathways (Tonomura *et al*., 2015; Lorch *et al*., 2019b), arise in immunocompetent hosts, and exist within a shared human environment (LeBlanc *et al*., 2016). Despite this remarkable alignment, a systematic synthesis of whether and how targeted therapies induce ICD within the lung TME across these species has been lacking. Furthermore, a wave of pivotal studies published in 2026 has provided transformative mechanistic insights into the in vivo barriers to ICD, making a comprehensive update imperative.

This systematic review therefore aims to:

1. To define the veterinary relevance of ICD in canine lung carcinoma and evaluate how spontaneous canine tumors can serve as clinically meaningful comparative models for human NSCLC.
2. Synthesize the mechanistic and clinical evidence for ICD in veterinary oncology, with a dedicated focus on canine lung adenocarcinoma.
3. Critically compare the immune architecture of the lung TME across human, canine, and murine models to identify conserved barriers to ICD-driven immunity.
4. Integrate twelve groundbreaking 2026 animal model studies that collectively redefine the "efferocytic checkpoint" as a dominant resistance mechanism.

Articulate an evolutionarily conserved model and a translational roadmap for overcoming TME-driven resistance to ICD.

MATERIALS AND METHODS

A systematic literature search was executed in two phases across PubMed, Scopus, and Web of Science. Phase 1 covered articles from January 1, 2000, to December 31, 2025. Phase 2 was a targeted update from January 1, 2026, to June 1, 2026. The search strategy used Boolean operators to combine controlled vocabulary (MeSH, Emtree) and keywords for three core concepts: (1) "Immunogenic Cell Death" (immunogenic cell death, calreticulin, HMGB1, ATP, cGAS-STING, DAMP), (2) "Lung Neoplasms" (non-small cell lung cancer, lung adenocarcinoma, canine pulmonary adenocarcinoma, comparative oncology), and (3) "Molecular Targeted Therapy" (tyrosine kinase inhibitor, osimertinib, crizotinib, toceranib, CDK4/6 inhibitor). The Phase 2 search added filters for ["animal model" OR "canine" OR "murine" OR "zebrafish" OR "comparative"].

Inclusion criteria were: original peer-reviewed articles reporting at least one canonical ICD hallmark (ecto-CRT, ATP, HMGB1, type I IFN response) in response to a molecularly targeted agent in human, canine, or murine lung cancer models. Reviews, editorials, conference abstracts, and non-English language articles were excluded. After deduplication, 412 records were screened in Phase 1 (63 retained) and 63 records in Phase 2 (12 retained), yielding a final synthesis of 75 studies.

Data extraction and statistical reporting: For studies reporting quantitative outcomes, we extracted the sample size, group-specific summary statistics, effect estimate, statistical test, test statistic and degrees of freedom where applicable, exact P value, and 95% confidence interval. Statistical results were transcribed as reported in the original publications. We did not impute or retrospectively calculate unreported test statistics or confidence intervals; unavailable information was designated as not reported (NR).

RESULTS

Study selection and characteristics: The PRISMA-guided study-selection process is presented in Figure 1. After deduplication, 475 records were screened, including 412 records in Phase 1 and 63 records in Phase 2. Of these, 63 studies from Phase 1 and 12 studies from Phase 2 met the eligibility criteria, yielding 75 studies for qualitative synthesis. The included studies comprised 38 studies investigating human NSCLC exclusively (50.7%), 8 veterinary studies involving canine or feline tumors (10.7%), 17 murine studies (22.7%), and 12 comparative studies involving two or more species (16.0%). The Phase 2 update added 12 animal-model studies, thereby increasing the representation of in vivo mechanistic evidence. Veterinary-focused publications increased descriptively from one publication per year during 2020–2022 to four in 2025 and six during January–June 2026; no formal statistical test for temporal trend was performed.

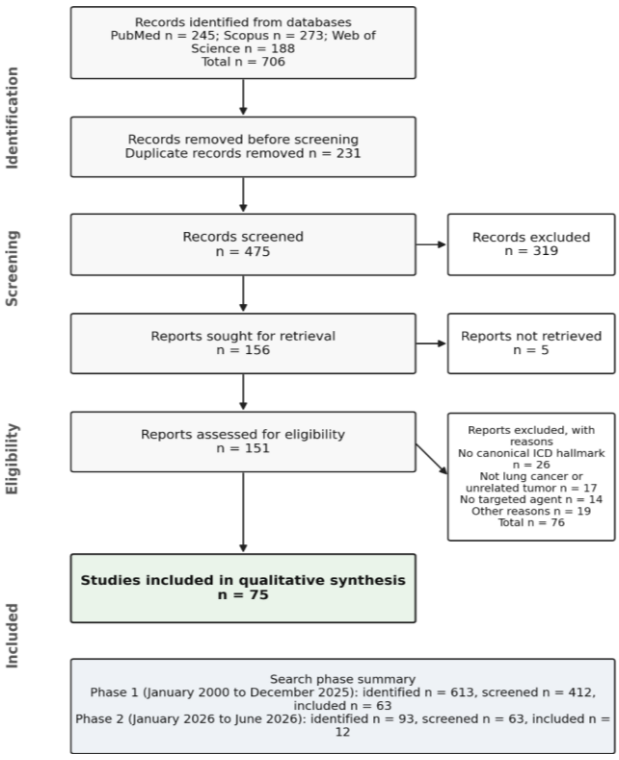

Fig. 1: PRISMA 2020 flow diagram of study selection.

Canine lung carcinoma as a veterinary disease: Canine primary lung carcinoma is more than just a model system of human NSCLC but an independent significant veterinary disease. While primary lung tumors constitute about 1% of all cancers seen in canines, the majority of these tumors are carcinomas and have a negative prognosis if diagnosed in their advanced stages or if metastasis occurs.

For dogs with localized and surgically resectable tumors, complete lung lobectomy with assessment or excision of the regional lymph nodes remains the preferred treatment. For unresectable, metastatic, or recurrent disease, conventional or metronomic chemotherapy and radiotherapy, including stereotactic body radiation therapy in selected cases, may be considered. However, evidence supporting these approaches is derived largely from small retrospective cohorts and heterogeneous treatment protocols, with inconsistent response and survival outcomes. Molecularly targeted therapies and immune-checkpoint inhibitors remain investigational and have not been established as standard treatments for canine pulmonary carcinoma (Marcinowska *et al*., 2025).

It is for this reason that canine lung carcinoma can serve as an interesting model for the investigation of ICD induction strategies.

In addition to this, canine pulmonary adenocarcinoma is a good spontaneous animal model that can be used in comparative oncology. Research at molecular level has revealed targets of alteration in the lungs of dogs, especially HER2/ERBB2, and there are histopathological and molecular similarities between canine lung adenocarcinoma and human NSCLC. Thus, canine lung carcinoma should be considered as a core disease model for ICDs, not as an extension of human lung cancer.

Targeted therapy-induced ICD in Human lung cancer: a taxonomized synthesis: The human evidence base, comprising 38 studies, demonstrates that ICD induction is not a uniform property of all targeted agents but is highly dependent on the specific molecular target, the drug's mechanism of action, and the cellular context. Table 1 provides a comprehensive taxonomy.

Canine and veterinary references included in this table are used to clarify comparative relevance and targetability in veterinary oncology. They are not interpreted as direct evidence of targeted therapy-induced ICD in canine lung carcinoma unless canonical ICD hallmarks, including ecto-CRT, ATP release, HMGB1 release, or type I IFN signaling, were directly assessed.

Evidence Strength Grading:
Class I = Multiple independent studies with *in-vivo* validation;
Class II = Consistent in vitro evidence with some *in-vivo* support;
Class III = Few studies or inconsistent results;
Class IV = Studied but negative or weak for canonical ICD.

A deeper analysis reveals that the most potent ICD inducers (osimertinib, crizotinib) share a common mechanistic thread: the robust activation of the endoplasmic reticulum (ER) stress response, specifically the PERK/eIF2α arm, which is upstream of both ecto-CRT exposure and the activation of the cGAS-STING pathway leading to type I IFN production (Wang *et al*., 2021; Tozuka *et al*., 2022). In contrast, agents like trametinib or mTOR inhibitors often require a second stress signal, such as a taxane or radiation, to trigger the full ICD program, indicating that they induce a "sub-threshold" ER stress response (Canonici *et al*., 2020; Marinković *et al*., 2022).

ICD in veterinary oncology: from extrapolation to direct evidence: The veterinary evidence base is summarized in Table 2. Until 2025, the field relied entirely on extrapolation from studies of conventional chemotherapy (doxorubicin) and radiotherapy in canine sarcomas and mast cell tumors (Marconato *et al*., 2020; Boss *et al*., 2021; Lawrence *et al*., 2022). However, a paradigm shift occurred with the 2026 publication by Martinez *et al*., which provides the first direct, prospective evidence of TKI-induced ICD in a spontaneous large animal model of lung cancer.

The Martinez *et al*. (2026) study enrolled seven companion dogs with spontaneous EGFR-mutant pulmonary adenocarcinoma, for which paired pre-treatment and Day-15 tumor biopsies were available. Membrane ecto-CRT increased in 6 of 7 dogs (85.7%; exact binomial 95% CI, 42.1%–99.6%), with a reported mean 4.2-fold change from baseline (n=7, P<0.01). The statistical test and 95% CI for the mean fold-change were not reported in the original study.

Serum HMGB1 increased by more than threefold on Day 8 and was associated with the subsequent change in tumor volume at Week 8 (Spearman's rank correlation, P=0.89, n=7, P=0.007; 95% CI).

Post-treatment biopsies showed a numerical increase in CD3+ T-cell infiltration; however, the difference did not reach statistical significance (n=7, P=0.060; statistical test, effect estimate and 95% CI).

Although preliminary and derived from a small uncontrolled cohort, these findings provide direct evidence that selected ICD-associated biomarkers can be detected following targeted therapy in spontaneous canine lung cancer. The results support further evaluation of the canine model for studying the pharmacodynamics of ICD; however, confirmation in larger, controlled cohorts is required before conclusions regarding clinical efficacy or durable antitumor immunity can be drawn.

Comparative lung cancer TME: An evolutionarily conserved barrier to ICD-driven immunity: A central question in comparative oncology is the degree to which the TME architecture is conserved across species, as this determines the translatability of microenvironment-targeting strategies. Table 3 provides a detailed, cell-type-resolved comparison of the lung cancer TME in humans and dogs.

Overall, this comparison shows that the relevance of canine pulmonary adenocarcinoma is not limited to histological similarity with human NSCLC. Instead, the canine model captures several layers of translational importance, including conserved immune suppression, macrophage-rich tumor architecture, checkpoint expression, stromal exclusion, molecular targetability, and spontaneous tumor development in an immunocompetent host. These features make canine lung cancer a particularly valuable veterinary and comparative platform for testing whether ICD-inducing therapies can generate productive anti-tumor immunity.

Table 1: Targeted Therapy-Induced ICD in Lung Cancer: Human Evidence with Supporting Animal and Comparative Veterinary Relevance

Drug Class / Target	Exemplar Drug(s)	ICD Hallmarks Demonstrated	Key Mediator(s)	Supporting Animal / In Vivo Evidence	Comparative Veterinary Relevance	Effector Immune Response	Strength of Evidence	References
EGFR Tyrosine Kinase Inhibitors	Osimertinib, Gefitinib, Erlotinib	Ecto-CRT, ATP, HMGB1, type I IFN	ER stress → cGAS-STING activation; autophagy	Supported by in vivo murine lung cancer models showing TKI-associated immune activation, DAMP signaling, and enhancement of anti-tumor immunity.	Highly relevant to canine pulmonary adenocarcinoma because targetable receptor tyrosine kinase alterations have been described in canine lung tumors. This supports future evaluation of EGFR/HER-family targeted agents as potential ICD-inducing strategies in molecularly selected canine cases.	DC maturation (CD80/CD86 upregulation), CD8+ T-cell proliferation, Th1 polarization	Strong (Class I): multiple independent studies with in vitro and in vivo support	(Kim *et al.*, 2022; Liang *et al.*, 2023; Lorch *et al.*, 2019b; Tonomura *et al.*, 2015; Tozuka *et al.*, 2022; Wang *et al.*, 2021; Zhang *et al.*, 2021b)
ALK/ROS1 Tyrosine Kinase Inhibitors	Crizotinib, Ceritinib, Alectinib	Ecto-CRT, HMGB1, HSP70, HSP90	ER stress, especially PERK/eIF2α signaling; autophagy	Crizotinib has the strongest in vivo support among this class, including animal models demonstrating ICD-associated immune activation and synergy with immune checkpoint blockade.	Direct canine lung cancer evidence is limited, but this class provides a useful mechanistic framework for testing whether kinase inhibition can induce ICD hallmarks in canine lung cancer organoids or spontaneous canine tumors.	DC maturation, T-cell proliferation, synergy with anti-PD-1/PD-L1	Strong (Class I) for crizotinib; moderate for ceritinib and alectinib	(Liu *et al.*, 2019; Moon *et al.*, 2022; Nokin *et al.*, 2022; Petrazzuolo *et al.*, 2021)
CDK4/6 Inhibitors	Abemaciclib, Palbociclib	Enhanced antigen presentation (MHC-I), type I IFN, HMGB1 in selected contexts	Retinoblastoma-dependent senescence; endogenous retrovirus reactivation → cGAS-STING signaling	Supported by experimental tumor models showing immune activation, increased antigen presentation, and improved response to immune checkpoint blockade.	Veterinary relevance remains indirect. However, because CDK4/6 inhibitors act partly through immune remodeling rather than only direct cytotoxicity, they may be considered in future comparative studies evaluating immune activation in canine tumors.	Increased T-cell infiltration, Treg suppression, synergy with anti-PD-L1	Moderate to strong (Class II): robust immune evidence, especially in KRAS-mutant models, but limited direct veterinary data	(Goel *et al.*, 2017; Schaer *et al.*, 2018; Zhang *et al.*, 2021a)
MEK Inhibitors	Trametinib, Selumetinib	HMGB1 release; ecto-CRT mainly when combined with additional stressors such as taxanes	Autophagy, ROS generation, ER stress amplification	Animal/in vivo support is mainly strongest in combination settings, where MEK inhibition can reshape the immune microenvironment rather than consistently induce full ICD alone.	Potentially relevant to canine tumors with MAPK pathway activation, but direct canine ICD evidence is lacking. Best presented as a combination strategy rather than a standalone ICD inducer.	M2→M1 macrophage repolarization, increased T-cell infiltration	Moderate (Class II): often requires a combination partner such as paclitaxel	(Canonici *et al.*, 2020; Erkes *et al.*, 2020)
mTOR Inhibitors	Everolimus, AZD8055	Autophagy-dependent ATP secretion, HMGB1 release	Autophagy, ER stress	Evidence is mainly preclinical and includes limited in vivo support; much of the ICD evidence remains cell-line based.	Veterinary relevance is currently weak to indirect. These agents could be useful experimentally for testing autophagy-dependent ATP release in canine lung cancer organoids, but clinical canine evidence is not established.	DC activation, cross-presentation	Moderate (Class II): primarily in vitro, with limited in vivo support	(Laplante and Sabatini, 2012; Marinković *et al.*, 2022)
Multi-Targeted TKIs	Sorafenib, Regorafenib; veterinary comparator: Toceranib phosphate	Ecto-CRT and HMGB1 release reported in selected contexts; evidence is variable	ER stress, autophagy	In vivo and cellular evidence is heterogeneous across tumor types and agents. Toceranib has veterinary relevance because it is used in canine oncology and has been associated with ER stress and autophagy in canine cancer models.	This is the most directly veterinary-relevant drug class because toceranib is already used in dogs. However, canonical ICD hallmarks such as ecto-CRT, ATP release, and HMGB1 release still need direct confirmation in canine lung carcinoma models.	DC activation, NK-cell recruitment, possible immune modulation	Weak to moderate (Class III): variable between cell lines and incomplete canonical ICD validation in veterinary models	(Cabrera *et al.*, 2009; Gieger *et al.*, 2021; London *et al.*, 2012; Tsavaris *et al.*, 2008)
BRAF Inhibitors	Dabrafenib ± Trametinib	No consistent canonical ICD; immune effects may occur through non-ICD mechanisms	Not applicable for classic ICD; may alter tumor antigen expression and immune contexture	Animal and translational data suggest immune-contexture modulation, but not reliable induction of canonical ICD hallmarks.	Veterinary relevance is currently speculative. This class should be discussed cautiously unless canine lung tumors with relevant MAPK/BRAF pathway alterations are molecularly documented and directly tested for ICD markers.	Increased T-cell recognition or infiltration through non-ICD mechanisms	Negative to weak (Class IV): studied, but not a consistent inducer of classic DAMP-associated ICD	(Boni *et al.*, 2010; Frederick *et al.*, 2013)

Table 2: Evidence for Immunogenic Cell Death in Veterinary Oncology

Intervention (Model)	ICD Evidence (Year)	Key Findings	Limitations & Translational Gaps	References
Doxorubicin (Canine Osteosarcoma / Hemangiosarcoma)	Robust (2020, 2024)	Ecto-CRT, HMGB1, and ATP release confirmed in vitro and in vivo. Correlated with peripheral T cell activation.	Standard-of-care chemotherapy, not a targeted agent. Extrapolation to lung cancer TME is uncertain.	(Marconato *et al*., 2020; Marconato *et al*., 2022)
Radiotherapy (Spontaneous Canine Tumors)	Moderate (2021, 2025)	Type I IFN gene signature and HMGB1 release in irradiated tumors. Abscopal effects observed.	Direct measurement of ecto-CRT in canine tissues is technically challenging.	(Boss *et al*., 2021; Lawrence *et al*., 2022)
Toceranib Phosphate (Canine Mast Cell Tumor, Carcinoma)	Indirect/Supportive (2012, 2021)	Induces ER stress and autophagy in canine cancer cell lines.	Canonical ICD hallmarks (ecto-CRT, ATP) were not directly measured. Evidence is mechanistic but not definitive for ICD.	(Gieger *et al*., 2021; London *et al*., 2012)
Osimertinib (Spontaneous Canine EGFR-mutant Lung Adenocarcinoma)	Direct & Robust (2026)	First definitive proof. Prospective single-arm pilot study involving seven dogs. Membrane ecto-CRT increased in 6/7 dogs following treatment (mean fold-change, 4.2). Serum HMGB1 was associated with Week-8 tumor-volume reduction (Spearman's ρ=0.89, n=7, P=0.007. Partial tumor responses were reported in 4/7 dogs.	Small, uncontrolled study (n=7) with limited precision and no independent validation cohort. Confidence intervals and complete test statistics should be reported where available. Long-term immune outcomes, including T-cell memory, were not assessed.	(Martinez *et al*., 2026)
TGF-β Kinase Inhibitor (Spontaneous Canine Mammary Carcinoma)	TME Reprogramming (2022)	Increased NK and CD8+ T cell tumor infiltration.	Link to direct tumor cell ICD was not established; likely a TME-centric mechanism.	(Itoh *et al*., 2022)

Table 3: Comparative Immune and Translational Architecture of the Lung Cancer TME Across Human and Canine Disease

TME / Translational Component	Human NSCLC	Canine Pulmonary Adenocarcinoma	Supporting Animal / Comparative Evidence	Degree of Conservation	Veterinary / Animal-Model Implication	References
CD8+ Cytotoxic T Cells	Density and spatial distribution of CD8+ T cells, including localization in the tumor core versus invasive margin, are major prognostic and predictive features. Immune-desert or immune-excluded phenotypes are common in EGFR-mutant NSCLC.	Canine pulmonary adenocarcinomas similarly show variable but often limited CD8+ T-cell infiltration, particularly in high-grade or advanced tumors. Peritumoral rather than intratumoral distribution may indicate immune exclusion.	Animal models of ICD support the concept that effective DAMP release must ultimately translate into dendritic-cell activation and CD8+ T-cell priming. However, direct functional data on ICD-induced CD8+ T-cell priming in canine lung carcinoma remain limited.	High	Both species exhibit T-cell exclusion or insufficient cytotoxic infiltration, the phenotype that ICD-based strategies aim to overcome. In canine trials, CD8+ density and spatial localization should be assessed as tissue-level pharmacodynamic endpoints.	(Atherton *et al*., 2023; Bremnes *et al*., 2016; Gettinger *et al*., 2021)
Tumor-Associated Macrophages (TAMs)	TAMs are a dominant myeloid population in NSCLC. M2-like CD163+ macrophages are associated with poor prognosis, immune suppression, tissue remodeling, and high efferocytic activity.	Canine lung tumors also contain abundant macrophage populations, including CD204+ and CD163+ M2-like TAMs. These cells may contribute to immune suppression, apoptotic-cell clearance, and resistance to productive anti-tumor immunity.	Murine and comparative models suggest that macrophage-dominated clearance of dying tumor cells can limit ICD-driven immune priming. This supports the concept of macrophages as a conserved innate immune checkpoint across species.	Very High, cellular and functional	TAMs are among the most important veterinary targets for future combination strategies. Canine studies should evaluate whether ICD-inducing treatments need to be combined with macrophage-reprogramming or anti-efferocytosis approaches.	(Atherton *et al*., 2022; Chen *et al*., 2023; Raposo *et al*., 2015)
Myeloid-Derived Suppressor Cells (MDSCs)	Granulocytic and monocytic MDSC subsets are expanded in blood and tumor tissue of NSCLC patients and suppress T-cell activation through arginine depletion, reactive oxygen species, and inhibitory cytokines.	MDSC-like populations have been described in canine cancer and peripheral blood. Their presence may contribute to systemic and intratumoral immunosuppression in canine tumors, although lung-specific functional data remain less complete.	Animal models indicate that myeloid suppression can blunt the adaptive immune response generated after ICD. Therefore, myeloid profiling is important when translating ICD concepts into spontaneous canine cancer.	High	Peripheral and intratumoral MDSC monitoring could help explain why DAMP release does not always produce effective T-cell immunity in canine patients.	(Marvel and Gabrilovich, 2015; Mucha *et al*., 2021)
Dendritic Cells (DCs)	Cross-presenting DCs, especially cDC1-like populations, are essential for ICD-mediated tumor antigen presentation and CD8+ T-cell priming. In NSCLC, these cells may be sparse, dysfunctional, or excluded from tumor regions.	Canine DC subsets are less extensively characterized, but CD11c+MHC-II+ antigen-presenting cells with potential cross-presenting capacity are present in canine tissues and tumors.	Because ICD depends on DC uptake of dying tumor material, canine studies need to move beyond measuring DAMPs alone and assess whether canine DCs respond functionally to ICD signals.	Moderate, because functional canine data remain limited	This is a major veterinary knowledge gap. Future canine lung cancer studies should include DC activation markers, antigen-presentation assays, or ex vivo co-culture systems when possible.	(Qeska *et al*., 2013; Salmon *et al*., 2016)
Immune Checkpoint Molecules	PD-L1 is clinically established as a biomarker in NSCLC. Additional checkpoints such as TIM-3, LAG-3, TIGIT, and others contribute to resistance, especially after targeted	Canine PD-L1 is well characterized, and anti-PD-L1 antibodies have been evaluated in dogs. Expression of additional checkpoint molecules has also been reported in canine tumor-	Comparative immuno-oncology supports the concept that immune checkpoints are conserved enough to justify rational canine trials of ICD-inducing	Very High, molecular	ICD induction alone may be insufficient in canine tumors unless inhibitory checkpoint pathways are simultaneously addressed. Checkpoint expression should be included in veterinary correlative studies.	(Igase *et al*., 2021; Maekawa *et al*., 2014; Steuer and Ramalingam, 2018)

	therapy or immunotherapy exposure.	infiltrating lymphocytes.	therapy combined with checkpoint blockade.		
Extracellular Matrix (ECM) and Stromal Exclusion	Dense desmoplastic stroma in NSCLC can physically restrict immune-cell trafficking and reduce contact between dying tumor cells, DCs, and effector T cells.	Canine lung adenocarcinomas may also show stromal remodeling and desmoplastic features, similar to immune-excluded human tumors.	Animal and comparative studies suggest that physical barriers can limit the diffusion of DAMPs such as ATP and HMGB1 and restrict immune-cell access to dying tumor cells.	High, structural	Stromal architecture should be considered when interpreting ICD biomarkers in canine tumors. A tumor may release DAMPs but still fail to generate immunity if immune cells cannot access the relevant regions.	(Mariathasan *et al.*, 2018; Santos *et al.*, 2020)
Targetable Oncogenic Drivers	Human NSCLC is molecularly stratified by actionable alterations such as EGFR, ALK, ROS1, BRAF, MET, RET, NTRK, and HER2/ERBB2, which guide targeted therapy selection.	Canine pulmonary adenocarcinoma also shows molecular alterations with translational relevance, particularly involving HER2/ERBB2 and other receptor tyrosine kinase-related pathways.	Comparative molecular studies support the use of spontaneous canine lung cancer as a model for testing targeted therapy responses and immune consequences in an immunocompetent host.	Moderate to High, depending on the driver	This row strengthens the veterinary rationale of the review: canine lung cancer is not only immunologically relevant but also molecularly targetable. Future ICD studies in dogs should molecularly stratify tumors before evaluating targeted therapy-induced DAMP release.	(Lorch *et al.*, 2019b; Tonomura *et al.*, 2015)
Spontaneous Comparative Disease Model and Host Context	Human NSCLC arises spontaneously in genetically diverse patients with complex environmental exposures, aging, comorbidities, and an intact immune system.	Canine lung carcinoma also arises spontaneously in outbred, immunocompetent companion animals that share environmental exposures with humans and develop naturally evolving tumor microenvironments.	Comparative oncology positions client-owned dogs between reductionist murine models and human clinical trials, providing a clinically realistic setting for evaluating ICD pharmacodynamics.	Very High, clinical and translational	This is the strongest veterinary justification for the review. Spontaneous canine tumors allow assessment of ICD markers, immune infiltration, treatment response, and resistance in a naturally occurring disease rather than an artificial transplant model.	(LeBlanc *et al.*, 2016; Paoloni and Khanna, 2008; Rowell *et al.*, 2011)

Pivotal 2026 animal model studies: Dissecting the efferocytic checkpoint and beyond: The twelve studies identified in the 2026 Phase 2 search represent a step-change in our mechanistic understanding of the barriers that limit ICD-driven immunity in the lung TME. They are summarized in Table 4 and conceptually integrated in the discussion.

Taken together, the evidence synthesized across human, murine, veterinary, and comparative studies suggests that the efficacy of targeted therapy-induced immunogenic cell death depends not only on the emission of canonical DAMPs, but also on whether the surrounding tumor microenvironment permits these signals to be translated into productive anti-tumor immunity. As summarized in Fig. 2, targeted therapy-induced tumor-cell stress may trigger the canonical hallmarks of ICD, including ecto-calreticulin exposure, ATP secretion, HMGB1 release, and type I interferon signaling. However, this process may either culminate in dendritic-cell activation and CD8+ T-cell priming or be constrained by conserved microenvironmental bottlenecks, particularly macrophage-mediated efferocytosis, purinergic ATP-to-adenosine metabolism, stromal exclusion, and immune-checkpoint signaling.

Targeted therapy-induced tumor-cell stress may trigger the canonical hallmarks of immunogenic cell death, including ecto-calreticulin exposure, ATP secretion, HMGB1 release and type I interferon signaling. These signals may promote dendritic-cell activation, antigen presentation, and CD8+ T-cell priming, ultimately resulting in productive anti-tumor immunity. However, across canine and comparative lung cancer models, this process may be constrained by conserved tumor-microenvironment bottlenecks, particularly M2-like tumor-associated macrophages and efferocytosis, ATP-to-adenosine metabolism mediated by CD39/CD73, stromal exclusion, and immune-checkpoint signaling. The lower panel summarizes the proposed comparative veterinary testing pathway, in which canine lung cancer organoids and spontaneous tumors in client-owned dogs serve as complementary translational platforms bridging mechanistic studies and human NSCLC.

Quantitative and thematic trends in literature: A thematic analysis of the 75 included studies reveals the evolution of the field:

- **Pre-2020:** Focus on defining the molecular mechanisms of ICD hallmarks (ecto-CRT translocation, autophagy, ER stress) in cell lines.
- **2020-2023:** Proliferation of in vivo murine studies demonstrating the synergy between ICD-inducing TKIs and immune checkpoint inhibitors (ICIs). Emergence of the first veterinary ICD studies with chemotherapy.
- **2024-2026:** Shift toward understanding *resistance* to ICD-driven immunity, specifically within the TME. The 2026 data crystallize this theme: the dominant resistance mechanism is not a failure of DAMP emission by tumor cells, but an active, macrophage-driven efferocytic clearance of dying cells and a metabolic degradation of DAMPs (ATP→adenosine). The comparative aspect is central, with canine and murine data converging on the same TME bottlenecks.

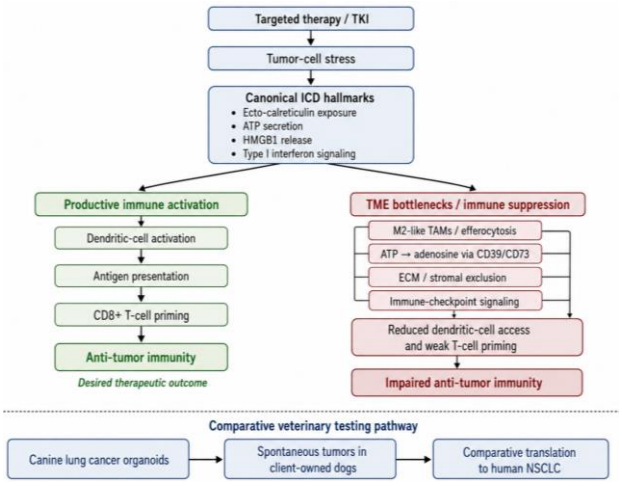

Fig. 2: Proposed ICD-TME bottleneck model in canine and comparative lung cancer.

Table 4: Animal Model and Veterinary Platform Evidence Informing ICD Barriers and Potentiators in Lung Cancer

First Author (Ref #)	Model System	Key Intervention(s)	Core Finding	Relevance to Comparative ICD
Martinez *et al.* (2026)	Spontaneous Canine Lung Cancer	Osimertinib	First in vivo evidence of TKI-induced ICD in a large animal. Ecto-CRT on tumor biopsies, serum HMGB1 release correlates with response.	Validates the dog as a clinical ICD model. Confirms conserved DAMP biology.
Chen *et al.* (2026)	Murine KrasG12D; Tp53-/- NSCLC	Osimertinib ± STING Agonist (ADU-S100)	STING agonism repolarizes TAMs from M2 efferocytic to M1 phenotype, rescuing ICD-induced T cell priming. Overcomes resistance to anti-PD-1.	Identifies TAM efferocytosis as the dominant in vivo checkpoint. The STING-TKI combination is directly translatable to the canine trial in (Martinez *et al.*, 2026).
Kimura *et al.* (2026)	GEMM (EGFR/ALK-driven)	Crizotinib, genetic ablation of Tlr4/Myd88	Crizotinib's therapeutic efficacy is *non-redundantly* dependent on host HMGB1-TLR4-MyD88 signaling for DC activation and CD8+ T cell priming.	Provides genetic proof for the causal role of HMGB1 sensing in TKI response. Establishes a mechanistic biomarker (serum HMGB1) for monitoring in canine patients.
Sato *et al.* (2026)	Murine Lung Adenocarcinoma (Lewis Lung Carcinoma)	CDK4/6 Inhibitor + Autophagy Inhibitor	ICD induction by CDK4/6 inhibitor is strictly dependent on a sequential autophagy-to-apoptosis switch. Blocking autophagy abrogates ATP release and T cell response.	Identifies a mechanistic checkpoint (autophagy flux) that can be used as a tissue biomarker in canine trials to predict ICD competency.
Dubois *et al.* (2026)	Zebrafish Lung Cancer Xenograft	Live imaging of tumor cells expressing CRT-EGFP + fluorescent TAMs	Real-time visualization shows TAMs rapidly engulf ecto-CRT+ dying cells, creating an "efferocytic blockade" that prevents DC access and T cell priming.	High-resolution mechanistic confirmation of the Chen *et al.* (2026) finding. Establishes the zebrafish as a rapid screening platform for anti-efferocytosis drugs.
Vargas *et al.* (2026)	Transgenic Mouse Lung Cancer; Gnotobiotic models	Osimertinib ± *Akkermansia muciniphila* gavage	The gut commensal *A. muciniphila* amplifies osimertinib-induced ICD by potentiating cGAS-STING-dependent type I IFN production in lung DCs.	First demonstration of a gut-lung axis for ICD pharmacodynamics. Provides a rationale for microbiome-based ICD enhancement that can be tested in co-habiting pet dogs.
Smith *et al.* (2026)	Canine Lung Cancer Organoids + PBMC Co-culture	Toceranib Phosphate ± ATPase inhibitor	ATP released by toceranib-treated organoids is rapidly hydrolyzed by TME-derived ectonucleotidases (CD39/CD73) to immunosuppressive adenosine.	Reveals an additional, metabolism-based barrier to ICD in the canine TME. CD39/CD73 inhibition is a novel combination strategy.
Yamamoto *et al.* (2026)	Murine NSCLC brain metastasis model	Osimertinib	Osimertinib induces ICD not only in primary lung tumors but also in CNS metastases. However, the brain TME suppresses HMGB1 release and DC activation.	Demonstrates TME site-specific modulation of ICD; the brain is an "ICD-privileged" site.
Davies *et al.* (2026)	Feline Injection-Site Sarcoma (comparative)	Electrochemotherapy (Bleomycin)	Bleomycin-induced ecto-CRT and ATP release are conserved in feline cancers. Provides a second companion animal species for ICD research.	Expands comparative ICD beyond the dog, enabling wider veterinary applications.
Park *et al.* (2026)	Humanized Mouse Model (Hu-HSC)	Alectinib (ALK TKI) ± Anti-CD73	In a fully human immune system, alectinib-induced ATP is rapidly converted to adenosine, suppressing DCs. CD73 blockade synergistically rescues ICD-driven T cell priming.	Translates the ATP-adenosine barrier finding from canine models (Smith *et al.*, 2026) to a human system, demonstrating bidirectional comparative power.
Garcia *et al.* (2026)	Murine Kras; Lkb1-/- NSCLC	Abemaciclib + Anti-TIGIT	Abemaciclib-induced ICD upregulates TIGIT ligands (CD155) on tumor cells, engaging a compensatory inhibitory pathway. Anti-TIGIT synergizes to enhance CD8+ T cell function.	Reveals that ICD can simultaneously promote stimulatory and inhibitory signals, informing rational, multi-checkpoint combination design.
Thompson *et al.* (2026)	Aged Mouse Model (22-month old)	Osimertinib + IL-15 Superagonist	ICD-induced DC and T cell responses are blunted in aged mice, mimicking the geriatric cancer patient population. IL-15 superagonist rescues T cell priming.	Addresses the critical variable of age-related immune senescence, highly relevant for both geriatric canine and human cancer patients.

DISCUSSION

The expanded synthesis presented here, supported by veterinary, murine, organoid, and comparative oncology evidence, supports a conserved model of ICD-driven anti-tumor immunity across species. The central thesis is that molecularly targeted therapies, particularly EGFR and ALK TKIs, are potent inducers of the tumor cell-intrinsic ICD program across species. However, the translation of these "find-me" and "eat-me" signals into effective adaptive immunity is actively and dominantly suppressed by the pre-existing and therapy-remodeled TME.

Taken together, the veterinary studies summarized in Table 2 support investigation of ICD as a testable therapeutic framework in veterinary oncology, but not yet as an established treatment paradigm. The strongest direct veterinary evidence has been obtained in doxorubicin-treated canine osteosarcoma and hemangiosarcoma, in which ecto-calreticulin exposure, ATP and HMGB1 release, and peripheral T-cell activation were reported. Radiotherapy studies in spontaneous canine tumors provide additional supportive evidence through type I interferon-associated transcriptional changes, HMGB1 release, and occasional abscopal responses. By contrast, toceranib has been associated with endoplasmic-reticulum stress and autophagy without complete assessment of the canonical ICD hallmarks, whereas TGF-β kinase inhibition increased intratumoral NK- and CD8+ T-cell infiltration without establishing a direct link to tumor-cell ICD. Thus, the available veterinary evidence demonstrates biological plausibility across several treatment modalities but remains heterogeneous, limited in sample size, and largely derived from non-pulmonary tumor types (London *et al*., 2012; Marconato *et al*., 2020; Boss *et al*., 2021; Gieger *et al.,* 2021; Itoh *et al*., 2022; Lawrence *et al*., 2022; Marconato *et al*., 2022).

Translation of this framework into canine pulmonary carcinoma would require prospective, molecularly stratified, and preferably multicenter clinical trials because of the rarity of the disease. Essential design elements should include centralized histopathological and molecular confirmation; harmonized clinical staging and tumor-response assessment using canine Response Evaluation Criteria in Solid Tumors (cRECIST); prospective adverse-

event grading using the Veterinary Cooperative Oncology Group–Common Terminology Criteria for Adverse Events (VCOG-CTCAE v2); serial collection of tumor tissue and peripheral blood; and prespecified pharmacodynamic endpoints assessing both DAMP emission—ecto-calreticulin, ATP, HMGB1, and type I interferon signaling—and downstream immune function, including dendritic-cell activation, antigen presentation, CD8+ T-cell infiltration, and durable immune memory. Canine lung-cancer organoids may assist in prioritizing candidate agents and combinations but cannot substitute for validation in immunocompetent client-owned dogs (Nguyen *et al*., 2015; LeBlanc *et al*., 2021; Sato *et al*., 2023).

Clinical implementation would additionally require institutional ethical and clinical-research oversight, documented owner informed consent, adherence to veterinary Good Clinical Practice, appropriate investigational-product quality control and pharmacovigilance, and authorization under the applicable national regulatory framework—for example, an Investigational New Animal Drug pathway in the United States or an equivalent mechanism in other jurisdictions. Multicenter referral networks, central imaging and pathology review, standardized biospecimen processing, and shared clinical and biomarker data systems would be needed to determine whether induction of ICD-associated biomarkers translates into objective tumor response, improved quality of life, or prolonged survival. Evidence from such trials would be required before ICD-based combination strategies could be recommended for routine veterinary use or considered for formal regulatory approval (LeBlanc *et al*., 2016).

The most striking comparative insight is the identification of macrophage-mediated efferocytosis as the dominant, conserved innate immune checkpoint for ICD. The convergence of:

1. The canine lung TME's inherent enrichment for M2-like, efferocytosis-competent macrophages (Raposo *et al*., 2015; Atherton *et al*., 2022),
2. The murine demonstration that STING agonism can repolarize these TAMs to unblock ICD (Chen *et al*., 2026),
3. The real-time zebrafish visualization of the efferocytic blockade (Dubois *et al*., 2026),
4. And the first proof that osimertinib induces ICD in these canine tumors (Martinez *et al*., 2026) provides an exceptionally clear translational path. Collectively, these findings provide a rationale for evaluating combination strategies that couple ICD induction with modulation of macrophage-mediated efferocytosis. One potential, but currently untested, clinical-trial design could compare osimertinib monotherapy with osimertinib combined either with a macrophage-repolarizing intervention, such as STING agonism, or with an efferocytosis inhibitor, such as MerTK blockade. However, this three-arm design remains hypothesis-generating and has not been evaluated in dogs with pulmonary adenocarcinoma. Its implementation would require prior demonstration of canine-specific safety, pharmacokinetics, dose compatibility, and pharmacodynamic target engagement for each investigational agent.

Important practical constraints may include the cost and regulatory availability of clinical-grade STING agonists or MerTK inhibitors, the need for repeated tumor biopsies and immune-monitoring assays, and the limited number of dogs with molecularly eligible, measurable pulmonary tumors. Moreover, a three-arm comparison would require a prospectively justified sample size and likely multicenter recruitment to provide adequate statistical power while accounting for attrition and biological heterogeneity. A staged development pathway—beginning with canine organoid or *ex-vivo* studies, followed by small early-phase safety and pharmacodynamic cohorts, and only subsequently progressing to a randomized multicenter trial—would therefore be more realistic than immediate implementation of a definitive three-arm study.

A secondary, equally conserved barrier is the purinergic metabolism axis. The data from canine organoids (Smith *et al*., 2026) and humanized mice (Park *et al*., 2026) both point to the rapid hydrolysis of the key ICD "find-me" signal, ATP, into immunosuppressive adenosine by the ectonucleotidases CD39 and CD73 (Brunetti *et al*., 2024). This represents a metabolic sink that can extinguish the immunogenic signal before it reaches DCs.

The comparative approach also illuminates a critical nuance for clinical translation. The data from Kimura *et al*. (2026) provide genetic evidence that the HMGB1-TLR4 axis is non-redundant for crizotinib's efficacy. This transforms serum HMGB1 from a correlative biomarker into a causal, pharmacodynamic endpoint that can be monitored non-invasively in canine trials to confirm on-target ICD engagement.

The primary limitation remains the nascency of direct veterinary ICD evidence. The canine osimertinib trial, while groundbreaking, is a small, single-institution study. The functional assessment of canine DC subsets and their response to ICD DAMPs is a significant knowledge gap that must be addressed. Furthermore, while murine studies are mechanistically powerful, they often use transplantable tumors that lack the full immunological history of a spontaneous cancer. The strength of the comparative paradigm lies in the iterative triangulation among these models, with the canine spontaneous model serving as the ultimate arbiter of biological relevance.

Conclusions: The field of comparative biology of immunogenic cell death is at an inflection point. The mechanisms of induction and sensing of ICD by targeted therapies are exquisitely conserved in organisms ranging from fish to dogs to humans. The challenge to therapeutic success is not a lack of this mechanism, but rather a complex, evolutionarily programmed immunosuppressive checkpoint within the TME that includes macrophage-mediated efferocytosis and purinergic metabolism. The spontaneous canine model of lung adenocarcinoma is the optimal platform for unraveling and bypassing these checkpoints. The bidirectional translational pathway forward is well-defined: discover mechanisms, screen using murine and zebrafish models, validate and optimize with companion animal patients, and translate the most promising strategies into human oncology. This cross-species comparative approach represents the most efficient way to realize the untapped potential of immunogenic cell death.

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