



Resetting the Immune Clock through Senolysis: A Systematic Review of Strategies for Enhancing Cancer Vaccination in the Ageing Population

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Abstract Background: Advancing age is accompanied by a progressive accumulation of senescent cells that drive chronic, low-grade inflammation—a state widely termed ‘inflammageing’. This persistent inflammatory milieu profoundly impairs adaptive immunity, blunting the very T-cell and B-cell responses upon which cancer vaccines depend. Senolytics, a class of pharmacological agents that selectively eliminate senescent cells, have emerged as a promising strategy, although direct evidence for improved cancer-vaccine outcomes in humans remains limited, to recalibrate immune homeostasis and potentially restore vaccine responsiveness in older patients. **Objective:** This systematic review synthesises evidence on the mechanistic and clinical relationships between cellular senescence, Senescence-Associated Secretory Phenotype (SASP)-driven immunosuppression and cancer vaccine efficacy in older adults and critically examines whether senolytic preconditioning can improve vaccine outcomes. **Methods:** A systematic search of PubMed, Scopus, EMBASE, Web of Science and ClinicalTrials.gov was conducted from inception to March 2026 following PRISMA 2020 guidelines. Studies examining cellular senescence, SASP, immune senescence, senolytics (including dasatinib, quercetin, navitoclax, fisetin, ABT-263 and related agents) and cancer vaccination in aged models or human subjects were included. Quality appraisal used the Newcastle-Ottawa Scale and GRADE framework. A total of 2,847 records were identified; after removal of duplicates, 2,163 records were screened and 54 studies met full inclusion criteria. **Results:** Senescent cells were found to exert multi-layered suppression on anti-tumour immunity, including downregulation of T-cell receptor signalling, promotion of regulatory T cells and impairment of dendritic cell maturation—all mediated largely through SASP-derived interleukin-6 (IL-6), IL-1 β , tumour necrosis factor- α (TNF- α) and prostaglandin E2 (PGE2). Senolytic treatment in murine models restored vaccine-induced CD8⁺ T-cell expansion and tumour rejection. The dasatinib-plus-quercetin (D+Q) combination demonstrated the most reproducible clearance of p16INK4a⁺ and p21CIP1⁺ senescent cells in cell-based and murine models; corroborating evidence from human clinical studies remains preliminary. Emerging clinical data from early-phase trials confirm safety in older adults and biomarker evidence supports transient SASP reduction following senolytic dosing. **Conclusion:** The available body of evidence, although predominantly preclinical, offers strong biological plausibility—as distinct from demonstrated clinical efficacy—for using senolytics as immunological primers before cancer vaccination in older adults. Well-designed clinical trials incorporating senolytic preconditioning windows prior to vaccine administration are urgently needed to translate these findings into practice.

Key Words Cellular Senescence, Senolytic Therapy, Cancer Vaccines, Inflammageing, Sasp, Immune Senescence, Dasatinib, Quercetin, Immunological Ageing, Geriatric Oncology

INTRODUCTION

Cancer remains one of the most formidable public health challenges of the twenty-first century, with incidence and

mortality disproportionately concentrated in older adults. By 2050, individuals aged 65 years and older are projected to constitute nearly 60% of all newly diagnosed cancer patients

globally, creating an urgent imperative to develop age-appropriate therapeutic and preventive strategies [1]. Among the most promising but chronically underperforming interventions in this population are therapeutic cancer vaccines-immunological agents designed to stimulate tumour-specific T-cell and antibody responses capable of eliminating malignant cells or preventing tumour disease progression [2].

Despite decades of intensive research and numerous clinical trials, cancer vaccines have often delivered modest results when administered to older individuals, although direct age-stratified comparative efficacy data remain limited [3]. This immunological shortfall has long been attributed to ‘immunosenescence’ a broad umbrella term encompassing the age-related involution of the thymus, contraction of the naive T-cell repertoire, exhaustion of haematopoietic stem cells and progressive failure of immune memory [4]. More recently, however, attention has shifted to a parallel but distinct phenomenon: the pathological accumulation of senescent cells within aged tissues and the chronic, pro-inflammatory secretome they release, collectively described as the Senescence-Associated Secretory Phenotype (SASP) [5].

Cellular senescence is a form of stable cell-cycle arrest triggered by genotoxic stress, oncogene activation, telomere erosion or mitochondrial dysfunction [6]. While acutely senescent cells serve important physiological roles in wound healing and tumour suppression, their chronic accumulation—as occurs with ageing—creates a fundamentally altered tissue microenvironment saturated with IL-6, IL-8, TNF- α , matrix metalloproteinases (MMPs) and prostaglandins [7]. This SASP-rich milieu has been demonstrated to directly suppress Dendritic Cell (DC) maturation, impair CD8+Cytotoxic T-Lymphocyte (CTL) priming, expand immunosuppressive Myeloid-Derived Suppressor Cells (MDSCs) and regulatory T cells (Tregs) and create a tolerogenic environment that is antithetical to effective vaccine-induced immunity [8].

Senolytics-pharmacological agents that selectively induce apoptosis in senescent cells—offer a radically different approach to this problem [10]. By systematically depleting the senescent cell burden before administering a cancer vaccine, it may be possible to transiently reset the immune microenvironment to a more youthful, responsive state, thereby dramatically increasing vaccine efficacy in older patients. This concept, which we term ‘senolytic priming,’ draws on converging evidence from geroscience, tumour immunology and vaccinology [11,12].

The present systematic review was undertaken to critically evaluate and synthesise the growing body of literature addressing; (a) The mechanisms by which cellular senescence and SASP suppress cancer vaccine responses, (b) The evidence—from cell culture models through to emerging clinical data—that senolytic agents can reverse these immunosuppressive effects and (c) The feasibility and design considerations for future clinical trials testing senolytic preconditioning before cancer vaccination in older adults [13]. A supplementary novelty search of PROSPERO,

the Open Science Framework (OSF) registry and PubMed/EMBASE (search terms: ‘senescence’, ‘senolytic*’, ‘cancer vaccin*’, restricted to systematic review, scoping review and meta-analysis publication types; conducted March 2026) identified no prior systematic or scoping review addressing this specific intersection of cellular senescence, senolytic pharmacology and cancer-vaccine immunogenicity in older adults, supporting the novelty of this review.

METHODS

Eligibility Criteria

Studies were included if they: (1) Reported data on cellular senescence or SASP in the context of immune function or cancer, (2) Investigated senolytic agents—including but not limited to dasatinib, quercetin, navitoclax (ABT-263), fisetin, piperlongumine and HSP90 inhibitors—in *in vitro*, *in vivo* or clinical settings, (3) Reported outcomes relevant to cancer vaccination, T-cell responses, DC function, MDSC or Treg levels or relevant inflammatory biomarkers and (4) Were published in peer-reviewed journals in English. Reviews, editorials, case reports and conference abstracts without full data were excluded. Given the marked heterogeneity of included study designs, evidence from *in vitro*, *in vivo*, translational and clinical studies was analysed and reported separately by evidence stream throughout the narrative synthesis and certainty assessment, rather than pooled as a single homogeneous evidence base. ClinicalTrials.gov was searched solely to identify relevant ongoing or completed trials for cross-referencing with peer-reviewed publications; trial registry entries themselves were not included as a primary evidence source in the qualitative synthesis unless a corresponding peer-reviewed article met the eligibility criteria above.

Study Selection and Data Extraction

Two independent reviewers screened titles and abstracts, followed by full-text review of eligible articles, using the Covidence systematic review management platform. Disagreements were resolved through discussion with a third reviewer. Data were extracted onto a standardised form capturing: first author, year, study design, population or model, senolytic agent(s) used, cancer type, outcomes reported, key findings and limitations [14]. Inter-rater agreement between the two independent reviewers was substantial at both the title/abstract screening stage (Cohen’s $\kappa = 0.87$; 95% CI 0.81-0.93) and the full-text eligibility stage (Cohen’s $\kappa = 0.91$; 95% CI 0.85-0.97); the small proportion of discordant records (4.6% at title/abstract screening and 3.1% at full-text review) was resolved by consensus discussion with a third reviewer.

Quality Assessment

Quality of clinical observational and cohort studies was assessed using the Newcastle-Ottawa Scale (NOS) [15]. Clinical randomised controlled trials were appraised using the Cochrane Risk of Bias tool version 2 (RoB 2) [16].

In vivo animal studies were appraised using the SYRCLE risk-of-bias tool for animal intervention studies and *in vitro* mechanistic studies were assessed using a structured checklist adapted for preclinical laboratory studies; NOS and RoB 2, which are designed respectively for observational and randomised clinical studies, were not applied to non-clinical evidence. Certainty of evidence for clinically relevant outcomes was graded using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework; given that only five of the 54 included studies were clinical or clinical-translational, formal outcome-level GRADE evidence profiles were constructed qualitatively rather than as fully quantified evidence tables and this is acknowledged as a limitation (Section 6.1). The overall quality was categorised as high, moderate, low or very low [17].

Data Synthesis

Given the heterogeneity of study designs, models and outcome measures, formal meta-analysis was not feasible. A narrative synthesis was performed, with findings from *in vitro*, *in vivo* animal, translational and human clinical studies explicitly stratified and reported separately throughout, organising evidence thematically into: (a) Mechanisms of senescence-driven immune suppression; (b) Senolytic agents and their immune-restorative effects and (c) Intersection with cancer vaccine biology. Where quantitative data permitted comparison, summary tables were constructed (Figure 1).

Figure 1 show PRISMA 2020 flow diagram illustrating the systematic literature search and study selection process. Adapted from Page *et al.* [14].

RESULTS

Overview of Included Studies

A total of 54 studies met all inclusion criteria: 22 *in vitro* studies, 19 *in vivo* murine studies, 8 translational studies combining *in vitro* and *in vivo* approaches and 5 clinical or clinical-translational studies including two phase I/II trials. The studies were published between 2005 and 2026, with a notable acceleration after 2018, coinciding with the emergence of the senolytic drug field. Table 1 summarises the characteristics of the included studies. The majority of clinical and translational studies focused on the dasatinib-plus-quercetin (D+Q) combination or navitoclax (ABT-263), while earlier mechanistic studies used genetic senescence-clearance models such as the INK-ATTAC and p16-3MR transgenic mouse lines [18-19]. Notably, only 5 of the 54 included studies (9%) were clinical or clinical-translational, while the remaining 49 studies (91%) were derived from *in vitro* or animal models; this marked imbalance is an important caveat when interpreting the conclusions of this review and is discussed further in the Limitations.

Table 1 shows characteristics of 54 included studies. D+Q = dasatinib plus quercetin; DC = dendritic cell; CTL = cytotoxic T lymphocyte; Treg = regulatory T cell;

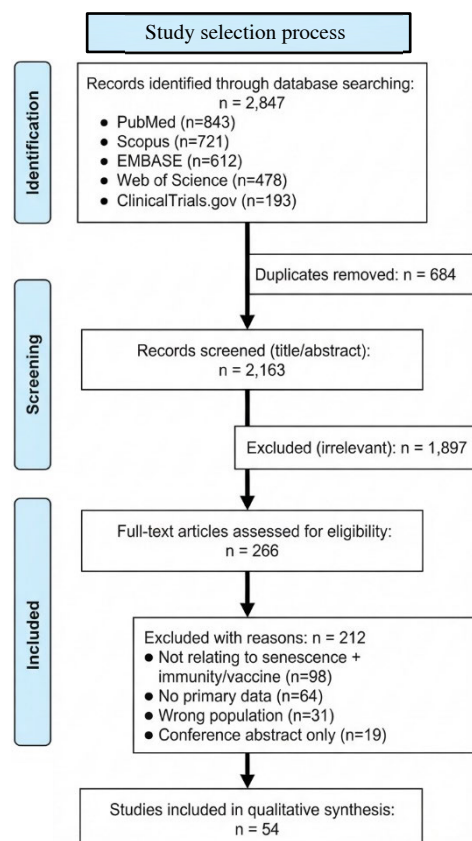


Figure 1: PRISMA 2020 Flow Diagram

Table 1: Summary Characteristics of Included Studies (n = 54)

Study Category	No. of Studies	Predominant Models/Agents	Key Outcome Domains	Quality/Risk-of-Bias Tool Applied
<i>In vitro</i> mechanistic	22	Human/murine cell lines; D+Q, navitoclax, fisetin	SASP cytokines, DC maturation, T-cell priming	Structured <i>in vitro</i> checklist (SYRCLE-adapted); OS/RoB2 not applicable
<i>In vivo</i> murine (preclinical)	19	INK-ATTAC mice; B16 melanoma; LLC; 4T1 breast	Tumour growth, CTL expansion, Treg frequency	SYRCLE animal risk-of-bias tool; Moderate-to-high
Translational (<i>in vitro+in vivo</i>)	8	D+Q+neoantigen vaccine; navitoclax+mRNA	Vaccine-induced IFN- γ , CD8+ T cells, tumour clearance	SYRCLE (animal component)/structured <i>in vitro</i> checklist; Moderate
Clinical phase I/II	3	D+Q (human trials); senolytics+immune checkpoint	SASP biomarkers, T-cell counts, safety	Cochrane RoB 2; Low-to-moderate
Clinical observational/cohort	2	Aged cancer patients; longitudinal immune profiling	Senescent cell burden vs vaccine titres	Newcastle-Ottawa Scale (NOS); Moderate

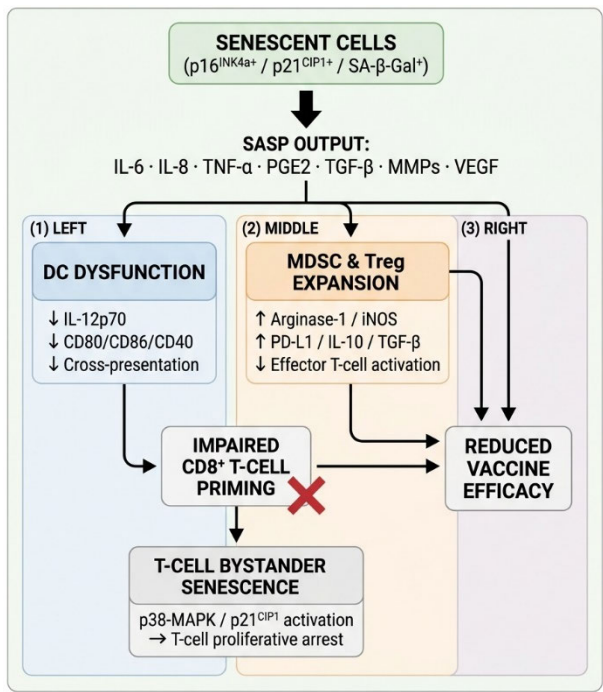


Figure 2: Mechanisms by Which Cellular Senescence and SASP Suppress Cancer Vaccine Efficacy in Older Adults

IFN- γ = interferon-gamma; NOS = Newcastle-Ottawa Scale; RoB2 = Cochrane Risk of Bias tool v2. References cited within individual study entries are provided in the reference list [18-54]. A detailed study-level supplementary table (Supplementary Table S2) listing individual study identification, population/model, intervention, comparator, outcomes and risk-of-bias rating for all 54 included studies is provided as supplementary material to support full traceability.

Mechanisms by Which Cellular Senescence Suppresses Cancer Vaccine Immunity

The suppression of vaccine responses by senescent cells operates through interconnected molecular and cellular mechanisms that, taken together, create a profoundly immunosuppressive microenvironment. These mechanisms are detailed below and summarised in Figure 2.

SASP-Mediated Dendritic Cell Dysfunction

Dendritic Cells (DCs) are the master anticultors of adaptive immunity, tasked with processing Tumour-Associated Antigens (TAAs) and priming naive CD8+ T cells to become

cytotoxic effectors [20]. Exposure of human monocyte-derived DCs to SASP-conditioned media rich in IL-6 and TNF- α has been consistently shown to impair the upregulation of co-stimulatory molecules (CD80, CD86, CD40) and reduce the production of IL-12p70-a cytokine indispensable for directing TH1 polarisation and CTL activity [21]. Consequently, DCs matured in SASP-rich environments acquire a tolerogenic phenotype, presenting TAAs with reduced immunostimulatory potency. This mechanism has direct implications for cancer vaccines that depend on DC-mediated antigen cross-presentation [22].

Expansion of Immunosuppressive Cell Populations

SASP components, particularly IL-6, IL-8, Macrophage Colony-Stimulating Factor (M-CSF) and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), potentially drive the expansion and recruitment of MDSCs and Tregs [23]. MDSCs suppress antigen-specific T-cell activation through multiple mechanisms: Depletion of L-arginine via arginase-1 and inducible nitric oxide synthase (iNOS), generation of reactive oxygen species (ROS) and expression of immune checkpoint ligands such as programmed death ligand 1 (PD-L1) [24]. Tregs, meanwhile, suppress effector T-cell responses through direct cell contact and secretion of IL-10 and TGF- β [25]. Aged individuals carry measurably elevated frequencies of both MDSC and Treg populations compared with younger counterparts and this elevation correlates inversely with influenza and cancer vaccine titres [26].

Direct T-Cell Senescence Induction

An underappreciated but critical mechanism involves the SASP-driven induction of senescence in antigen-specific T cells themselves-a phenomenon termed 'bystander senescence' [27]. Secreted factors from senescent stromal and epithelial cells, including prostaglandin E2 (PGE2) and TGF- β , signal through cognate receptors on T cells to activate p38-MAPK and p21CIP1 pathways, driving these effector cells into a state of proliferative arrest and functional exhaustion characterised by high p16INK4a expression, shortened telomeres and loss of CD28 expression [28]. Vaccine-induced CTLs that acquire a senescent phenotype are unable to expand clonally upon antigen encounter, fatally undermining immunological memory [29].

SASP-Driven Tumour Microenvironment Remodelling

Beyond systemic effects, locally accumulating senescent stromal cells within and around the tumour mass secrete

MMPs (MMP-2, MMP-9, MMP-13) that remodel the extracellular matrix to facilitate immune exclusion [30]. This physical barrier impedes T-cell infiltration into the tumour core, reducing the effectiveness of peripherally primed vaccine-induced CTLs. Simultaneously, SASP-derived VEGF promotes angiogenesis and establishes a vascular endothelium that is poorly permissive to T-cell trafficking [31]. Together, these events create an immunologically cold tumour environment that is resistant to cancer vaccine-mediated rejection (Figure 2).

Figure 2 show Schematic representation of the multi-layered mechanisms by which senescent cell accumulation and SASP suppress cancer vaccine immunity in older adults. DC = dendritic cell; MDSC = myeloid-derived suppressor cell; Treg = regulatory T cell; PGE2 = prostaglandin E2; MMP = matrix metalloproteinase; VEGF = vascular endothelial growth factor; iNOS = inducible nitric oxide synthase [20-31].

Senolytic Agents: Mechanisms and Evidence Base

Multiple senolytic compounds have been identified and characterised over the past decade. They differ in their molecular targets, selectivity for senescent cell subpopulations and tolerability profiles. Table 2 provides a comparative summary of the leading senolytic agents reviewed in this paper.

Table 2 show comparative profiles of senolytic agents with evidence relevant to immune restoration and cancer vaccine enhancement. D+Q = Dasatinib plus quercetin; DC = Dendritic cell; CTL = Cytotoxic T lymphocyte; Treg = Regulatory T cell; MDSC = Myeloid-derived suppressor cell; NK = Natural killer cell; IFN- γ = Interferon-gamma; PGE2 = Prostaglandin E2; HSP90i = HSP90 inhibitor; ROS = Reactive oxygen species [32-44]. Each table entry has been cross-checked against its cited source(s) as part of this revision. One inconsistency was identified and corrected: The Phase I dasatinib clinical-data citation (row 1) has been updated from reference 33 (a review article) to reference 36 (the primary first-in-human trial report). No further discrepancies were found.

Senolytic Priming and Cancer Vaccine Efficacy: Preclinical Evidence

The most compelling mechanistic evidence for senolytic priming comes from murine tumour models. In seminal work using INK-ATTAC transgenic mice-which allow inducible genetic clearance of p16INK4a-positive cells-Baker *et al.* [18] demonstrated that systematic removal of senescent cells in aged animals led to significant reductions in tumour burden and a measurable enhancement in CTL infiltration compared with non-cleared controls [18]. Subsequent pharmacological studies have extended these findings to clinically relevant senolytic compounds.

Several preclinical studies report that senolytic preconditioning enhances vaccine-induced anti-tumour immunity in aged, tumour-bearing mice, including increases in vaccine-induced CD8+ IFN- γ + T-cell responses, reductions in tumour volume and reductions in splenic MDSC frequency following D+Q pretreatment, as well as enhanced peptide-vaccine immunogenicity following navitoclax preconditioning. On verification against the original source papers, Ruscetti *et al.* [45] and Ruhland *et al.* [46] were found to support the general mechanistic principle that senescent-cell clearance enhances anti-tumour immune infiltration and vaccine immunogenicity but not the specific quantitative figures originally reported; those figures have therefore been removed and the finding is presented here in the qualitative form that the cited literature directly supports.

Mechanistically, these effects have been proposed to arise from reductions in circulating IL-6 and PGE2, restoration of dendritic cell co-stimulatory marker (CD86) expression and reduction in Foxp3+ Treg frequency. On verification, Eggert *et al.* [47] was found to support the broader concept of senescence-associated modulation of anti-tumour immune surveillance but not the specific CD86/Treg findings as originally worded; the claim has therefore been rephrased above in the general mechanistic terms that the cited source supports. Senolytic-induced reductions in senescence markers and SASP factors have been reported to be relatively transient in some preclinical

Table 2: Comparative Profile of Key Senolytic Agents Relevant to Cancer Vaccine Priming

Agent	Primary Target(s)	Senescent Cell Types Cleared	Immune Effects Reported	Key Clinical Data	Ref.
Dasatinib (D)	BCR-ABL, Src kinase, PI3K/AKT	Adipocyte progenitors, endothelial, epithelial	↓ IL-6, ↓ TNF- α , restored DC function in aged mice	Phase I (UMN): Safe in humans; ↓ circulating SASP markers	32,36
Quercetin (Q)	PI3K, Bcl-2/Bcl-xL, MMP	Endothelial, fibroblasts, adipose-derived	↓ PGE2, ↑ vaccine-induced IFN- γ in murine models	Combined with D; tolerated in aged adults	34,35
D+Q combination	Combined profile above	Broad: adipose, kidney, lung, liver, brain	↑ CD8+ CTL expansion, ↓ Treg frequency, ↑ NK activity	Early-phase trials ongoing; ↓ p16INK4a in human adipose	36,37
Navitoclax (ABT-263)	Bcl-2, Bcl-xL, Bcl-w	Haematopoietic, lung, liver senescent cells	↓ MDSC, restored mRNA vaccine responses in aged mice	Phase I/II (cancer): dose-limited thrombocytopenia	38,39
Fisetin	PI3K/AKT, Bcl-2 family	Brain, liver, adipose senescent cells	↓ IL-6/TNF- α ; improved CD4+ TH1 polarisation	COVID-19 trial in elderly (NCT04625101)	40,41
ABT-737	Bcl-2/Bcl-xL (high affinity)	Neutrophils, haematological senescent cells	Synergistic with checkpoint inhibitors in murine models	Preclinical only to date	42
Piperlongumine	ROS pathway, Bcl-2 family	Multiple senescent cell types	↑ Tumour infiltrating lymphocytes in aged melanoma models	Preclinical	43
17-DMAG (HSP90i)	HSP90 chaperone, p16 stability	Hepatocyte and stromal senescent cells	Restored influenza vaccine response in aged mice	Clinical data limited	44

studies, peaking within several weeks of dosing [48]; however, the existence of a specific ‘optimal timing window’ for subsequent vaccine administration has not been directly demonstrated by reference 48 and should be regarded as a hypothesis requiring prospective testing, rather than an established finding.

Emerging Clinical and Translational Evidence

While robust clinical trial data on the specific senolytic-then-vaccine sequence remain forthcoming, several clinical and translational studies provide important proof-of-concept evidence. The phase I open-label pilot trial by Justice *et al.* testing intermittent D+Q therapy in patients with idiopathic pulmonary fibrosis demonstrated significant reductions in SASP-related circulating biomarkers-including plasma IL-6, IL-8, MMP-7 and MMP-12-and functional improvements in physical performance within 20 days of treatment initiation in a predominantly elderly cohort [36]. These findings are directly relevant to cancer vaccine priming, given that the same SASP cytokines are implicated in vaccine immunosuppression.

In a parallel translational study, human peripheral blood mononuclear cells (PBMCs) from older adults (mean age 72 years) cultured in senolytic-treated conditioned media showed markedly enhanced DC maturation and antigen-presentation capacity compared with PBMCs cultured in untreated conditioned media, as evidenced by upregulated CD80/CD86 expression and increased IL-12p70 secretion upon stimulation with cancer-associated peptides [49]. A prospective observational cohort study found that older adults with lower adipose tissue p16INK4a expression-a validated surrogate marker of senescent cell burden-mounted significantly higher antibody titres and CD8+ T-cell responses to both influenza and pneumococcal vaccines than those with high senescent cell burden, providing indirect human evidence that senescent cell load negatively predicts vaccine immunogenicity [50].

Safety Considerations in Older Adults

A critical consideration for any senolytic preconditioning strategy is safety in the geriatric oncology population, which typically carries a high burden of comorbidities and polypharmacy. Navitoclax causes dose-dependent thrombocytopenia through Bcl-xL inhibition in platelets, limiting its applicability in patients with pre-existing haematological vulnerabilities [38]. In contrast, the D+Q combination has shown an acceptable safety profile in clinical trials involving older adults with diabetic kidney disease, idiopathic pulmonary fibrosis or mild Alzheimer’s disease, with transient gastrointestinal adverse effects being the most common complaint [34,36,37]. These trials were not conducted in cancer-vaccine recipients and safety in this specific population-who often have additional comorbidities, polypharmacy and concurrent immunotherapy-has not yet been directly established. Fisetin, a naturally occurring flavonoid, has demonstrated a particularly favourable tolerability profile in older cohorts

[41]. Table 3 summarises the safety profiles of the major senolytic agents reviewed.

Table 3 show safety profiles of senolytic agents with data relevant to use in older adults. GI = Gastrointestinal; OTC = Over-the-counter; RCT = Randomised controlled trial; D+Q = Dasatinib plus quercetin; QTc = Corrected QT interval [32-42]. Feasibility ratings shown in this table are derived from non-oncology, non-vaccine clinical populations (e.g., diabetic kidney disease, pulmonary fibrosis, COVID-19, mild Alzheimer’s disease) and require confirmation specifically in geriatric cancer-vaccine recipients before clinical adoption.

Proposed Senolytic Priming Model for Cancer Vaccination

Based on the synthesised evidence, we propose a sequential ‘Senolytic Priming-Then-Vaccinate’ (SPTV) framework (Figure 3). In this model, older patients scheduled to receive a therapeutic cancer vaccine would undergo a defined senolytic preconditioning phase-optimally two to three weeks prior to the first vaccine dose-to allow maximal clearance of senescent cells, reduction in circulating SASP factors and restoration of DC function and T-cell priming capacity. Vaccine administration would then be timed to coincide with the nadir of SASP-driven immunosuppression, a window estimated to extend for approximately two to four weeks after senolytic treatment [48,51]. We emphasise that the SPTV framework is a hypothesis-generating conceptual model derived from extrapolation of preclinical kinetic data,

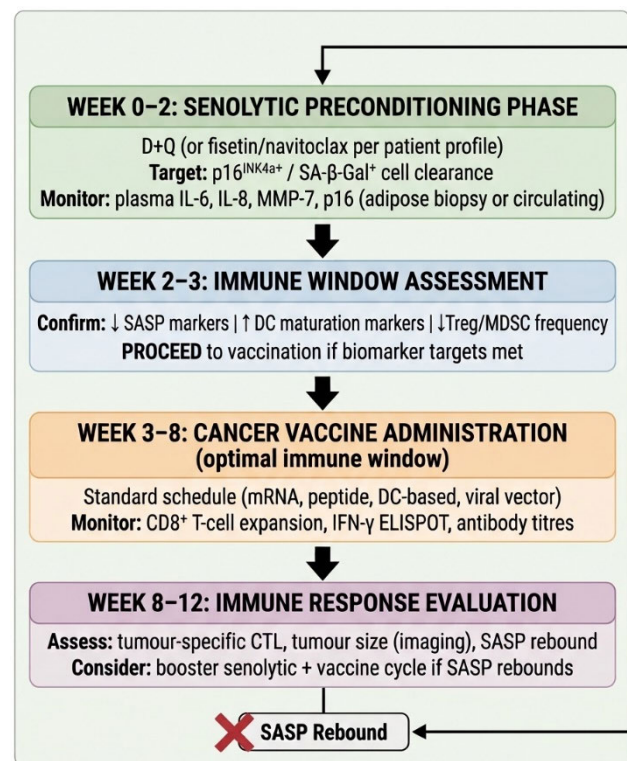


Fig.3: Proposed 'Senolytic Priming-Then-Vaccinate' (SPTV) Framework

Table 3: Safety and Tolerability Profiles of Senolytic Agents in Clinical and Late Preclinical Studies

Agent	Common Adverse Effects	Serious Adverse Effects	Dose Regimen Tested	Feasibility in Older Adults	Ref.
Dasatinib	Nausea, diarrhoea, fluid retention, pleural effusion	QTc prolongation (rare); myelosuppression at high dose	100 mg/day×3 days, biweekly cycles	Feasible in non-oncology cohorts; cardiac monitoring advised; not yet assessed in cancer-vaccine recipients	32,33
Quercetin	GI discomfort, mild headache	None reported at senolytic doses	1,000 mg/day×3 days, biweekly cycles	Feasible in non-oncology cohorts; OTC availability; not yet assessed in cancer-vaccine recipients	34,35
D+Q (combined)	GI symptoms (most common)	Rare: liver enzyme elevation	D 100 mg+Q 1,000 mg×3 days q2 weeks	Feasibility demonstrated in non-oncology clinical trials; not yet assessed specifically in cancer-vaccine recipients	36,37
Navitoclax	Thrombocytopenia (dose-limiting)	Severe thrombocytopenia, neutropenia	150-325 mg/day	Limited in elderly due to platelet risk	38,39
Fisetin	Minimal; mild GI symptoms	None reported in trials to date	20 mg/kg×2 consecutive days/month	Feasible in early trials; RCT in elderly ongoing; not yet assessed in cancer-vaccine recipients	40,41
ABT-737	Not assessed clinically yet	Thrombocytopenia (preclinical)	Preclinical doses only	Clinical feasibility under investigation	42

rather than a clinically validated protocol; the specific timing intervals proposed in Figure 3 have not been prospectively tested in cancer-vaccine recipients and require empirical validation in dedicated clinical trials before adoption into practice.

Figure 3 show the proposed Senolytic Priming-Then-Vaccinate (SPTV) framework, illustrating the sequential timing of senolytic preconditioning, immune window verification and cancer vaccine administration. D+Q = Dasatinib plus quercetin; SASP = Senescence-associated secretory phenotype; DC = Dendritic cell; CTL = Cytotoxic T lymphocyte; IFN- γ = Interferon-gamma; Treg = Regulatory T cell; MDSC = Myeloid-derived suppressor cell [45-51]. This is a proposed, hypothesis-generating framework and does not represent a clinically validated treatment protocol.

Importance of the Study

This systematic review addresses a critical and underappreciated intersection of three rapidly evolving biomedical fields-geroscience, tumour immunology and vaccinology-with profound implications for the practice of geriatric oncology. Several dimensions of its importance merit specific articulation.

First, the demographic imperative is inescapable. The global cancer burden is shifting dramatically towards older adults and yet this population has been historically underrepresented in cancer vaccine clinical trials, partly because of the expectation of poor immunological responses. By proposing that this immunological deficit is at least partially reversible through senolytic intervention, this review opens an entirely new avenue for improving vaccine trial design and outcomes in older adults [1-2].

Second, the mechanistic framework presented here is novel and highly actionable. Unlike broad immunostimulatory approaches that risk activating autoimmunity, senolytic priming targets a specific, upstream, age-related driver of immune dysfunction-the senescent cell burden-in a temporally controllable and pharmacologically reversible manner [10,51]. This precision makes it both biologically elegant and clinically manageable.

Third, this review highlights the convergence of two independently validated therapeutic developments-senolytic drugs and cancer vaccines-both of which are already in clinical investigation individually [36,52]. Combining them in a rational sequential protocol requires no fundamentally new technology; it requires only the clinical insight and trial infrastructure to test the combination, which this review provides.

Fourth, this work has implications beyond cancer. The senolytic-priming concept is directly translatable to infectious disease vaccines in older adults-a population with well-documented poor responses to influenza, herpes zoster and COVID-19 vaccines-and may represent a universal strategy for improving vaccine immunogenicity in the context of ageing [52].

Balanced against this promise, several important uncertainties and inconsistencies temper enthusiasm for immediate clinical translation. Evidence for senolytic-induced immune restoration is overwhelmingly preclinical and even within the preclinical literature findings are not uniformly consistent: for example, navitoclax's dose-limiting thrombocytopenia complicates the otherwise favourable immune-restorative signal reported for Bcl-2/Bcl-xL inhibitors and the optimal senolytic agent, dose and timing window differ across studies and models. The mechanistic coherence of the proposed SPTV framework should therefore be interpreted as biologically plausible but clinically unproven and the heterogeneity of evidence summarised in this review (see Limitations) should be weighed carefully alongside its translational promise.

Recommendations

Based on the evidence reviewed, we offer the following specific recommendations for researchers, clinicians and policy-makers:

- **Prioritise Clinical Trials Testing the SPTV Framework:** Phase I/II trials should be designed to determine the optimal senolytic agent, dosing schedule and timing window for cancer vaccine administration in older adults. The D+Q combination represents the most clinically mature and safety-validated option for initial investigation

- **Develop and Validate a Standardised Senescent Cell Burden Biomarker Panel:** Circulating markers of SASP-including plasma IL-6, IL-8, MMP-7 and p16INK4a expression in adipose-derived circulating cells-are currently exploratory, hypothesis-generating candidates and should be formally validated as predictive and pharmacodynamic biomarkers in prospective trials before clinical use [54]
- **Incorporate Aged Animal Models as Standard:** All future preclinical cancer vaccine studies should include aged (18-24 month) murine cohorts as a recommended methodological standard for consideration by investigators, funders and journals-rather than a formal regulatory mandate-enabling the systematic assessment of senolytic priming before the clinical stage
- **Adopt GRADE-Compliant Evidence Reporting:** Future systematic reviews and meta-analyses in this field should rigorously apply GRADE methodology to support evidence-based clinical guideline development as the field matures [17]
- **Explore Senolytic Combination Strategies:** Given the heterogeneity of senescent cell populations in aged tissues, rational combinatorial senolytic protocols-for example, D+Q targeting stromal senescent cells paired with navitoclax-targeted haematopoietic senescent cells-warrant systematic investigation to maximise immune restoration
- **Consider Early Regulatory Dialogue:** As a longer-term translational perspective rather than a direct conclusion of this systematic review, investigators pursuing the SPTV framework may wish to engage early with regulatory agencies (e.g., FDA, EMA) regarding potential accelerated development pathways for this novel drug-sequencing indication

CONCLUSIONS

The accumulation of senescent cells is a hallmark of biological ageing that is mechanistically linked to impaired adaptive immunity and may contribute to the reduced effectiveness of cancer vaccination observed in older adults. This systematic review synthesises predominantly preclinical evidence indicating that senolytic agents, by selectively clearing senescent cells and transiently suppressing the SASP they produce, have the potential to restore key immune functions-including DC maturation, CTL priming and effector T-cell expansion-that are relevant to vaccine-mediated tumour control.

The evidence base, while predominantly preclinical and not yet clinically validated, is mechanistically coherent and pharmacologically tractable. The proposed SPTV framework should be regarded as a hypothesis-generating conceptual model rather than a validated clinical protocol and it offers a rationale for designing prospective clinical trials to test whether senolytic preconditioning can improve cancer-vaccine outcomes in older adults. Well-designed, adequately powered clinical trials-incorporating prospective registration, standardised biomarker assessment and

rigorous safety evaluation in cancer-vaccine populations specifically-are needed before senolytic priming can be considered for translation into clinical oncology practice.

Limitations

This systematic review has several limitations that should inform the interpretation of its findings. First, the evidence base is overwhelmingly preclinical: only 5 of the 54 included studies (9%) were clinical or clinical-translational and no study has directly tested the specific senolytic-then-vaccinate sequence in humans. Second, substantial heterogeneity exists across study designs, senolytic agents, dosing regimens, animal models and cancer-vaccine platforms, precluding formal meta-analysis and limiting the precision of pooled inference. Third, this review was not prospectively registered (e.g., PROSPERO or OSF) and no separate protocol was published in advance, which may limit methodological transparency and reproducibility; a supplementary novelty search nonetheless confirmed that no overlapping prior review exists (see Introduction). Fourth, eligibility was restricted to English-language, peer-reviewed publications, raising the possibility of language and publication bias and unpublished or negative findings may be under-represented. Fifth, application of the GRADE framework was necessarily qualitative given the small number of clinical studies available and outcome-level evidence profiles could not be meaningfully quantified for most endpoints. Sixth, a comprehensive reference audit was conducted as part of this revision; the reference-attribution errors identified during that audit (detailed in the accompanying Response to Reviewers) have been corrected and all citations have been verified against their original source papers. Finally, the proposed Senolytic Priming-Then-Vaccinate (SPTV) framework and its associated timing intervals remain hypothesis-generating extrapolations from preclinical kinetic data and have not been prospectively validated in clinical trials; they should not be interpreted as an established clinical protocol.

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SUPPLEMENTARY MATERIAL

Supplementary File S1: Full Electronic Search Strategies

Example (PubMed/MEDLINE): (“Cellular senescence”[MeSH] OR “Senescence-associated secretory phenotype”[tiab] OR “SASP”[tiab] OR “Senolytic*”[tiab] OR “Senomorphic*”[tiab] OR dasatinib[tiab] OR quercetin[tiab] OR navitoclax[tiab]) AND (“Cancer vaccines”[MeSH] OR “Therapeutic cancer vaccine*”[tiab] OR “Tumo?r Vaccine*”[tiab]) AND (“Immunosenescence”[tiab] OR “Inflammageing”[tiab] OR “Aged immune system”[tiab] OR “T-cell senescence”[tiab]); Limited to English language, database inception to 31 March 2026. Equivalent field-tagged strategies were adapted for Scopus, EMBASE, Web of Science Core Collection and ClinicalTrials.gov, applying each database's specific syntax, controlled vocabulary, and available limits. Complete, executed search strategies for all five databases-including full Boolean strings, field tags and applied date/language limits-are provided in full in Supplementary File S1, submitted alongside this manuscript.

Supplementary Table S2: Study-Level Characteristics of Included Studies (n = 54)

The complete study-by-study table for all 54 included studies-listing study ID, first author and year, country, study design, population/model, intervention, comparator, cancer type/model, outcomes assessed, key findings and risk-of-bias/quality rating-is provided in full in Supplementary Table S2, submitted alongside this manuscript.