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The Role of Immunotherapy in Solid Malignancies: Biological Rationale, Clinical Evidence and Future Directions

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Abstract

Immunotherapy—especially immune checkpoint inhibitors (ICIs)—has reshaped the therapeutic landscape of solid tumors by restoring antitumor immunity through blockade of the programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) axes. The mechanistic foundation of ICI efficacy includes reversal of T-cell exhaustion, enhancement of antigen presentation, and remodeling of the tumor immune microenvironment (TME). Clinically, immune checkpoint blockade has expanded from early successes in melanoma and lung cancer to become integral across gastrointestinal, hepatobiliary, renal, gynecologic, breast, and molecularly selected colorectal cancers, with accelerating incorporation into perioperative and curative-intent strategies. Yet, broad benefit remains constrained by primary and acquired resistance, imperfect biomarkers, and immune-related adverse events (irAEs). This review synthesizes biologic principles, pivotal and contemporary trial evidence, and evolving clinical applications across major solid tumor groups, with emphasis on recent perioperative advances (2023–2025), circulating tumor DNA (ctDNA)-guided concepts, microbiome influences, combination immunotherapy strategies, and emerging cellular and adoptive immunotherapies. We highlight practical biomarker frameworks, toxicity recognition/management, and future directions that include next-generation checkpoints, engineered cell therapies, microbiome modulation, and adaptive treatment paradigms to extend durable benefit safely and equitably.

Keywords: Immune Checkpoint Inhibitors, PD-1, PD-L1, CTLA-4, Tumor Microenvironment, Biomarkers, ctDNA, Microbiome, Neoadjuvant Immunotherapy, Perioperative Immunotherapy, Adoptive Cell Therapy, TIL, CAR-T, Immune-Related Adverse Events

1. Introduction

Cancer progression is inseparable from immune escape. While early conceptual models proposed immune surveillance as a barrier to malignant transformation, tumors evolve "immune editing" strategies that permit growth despite host immunity. Modern immunotherapy leverages this biology: instead of directly killing tumor cells (as with cytotoxic therapy), it aims to re-enable effective immune recognition and elimination.

The clinical turning point came with immune checkpoint blockade. Sharma and Allison articulated the therapeutic logic that inhibitory checkpoints are actionable "brakes" on antitumor T-cell responses, and that checkpoint blockade can produce deep, durable remissions distinct from chemotherapy response patterns [1]. Ribas and Wolchok further emphasized that the signature of checkpoint therapy is the potential for durability, including long-term survival in subsets of patients across multiple tumor types, and the need to reframe response kinetics and endpoints accordingly [2].

Mechanistically, immunotherapy can be anchored to the "cancer-immunity cycle," in which effective antitumor immunity requires coordinated antigen release, presentation, priming, trafficking, infiltration, recognition, and killing [3]. Tumors can interrupt this cycle at many steps, which explains heterogeneity in response and provides a rationale for combination approaches that target multiple barriers simultaneously. The centrality of the TME—its immune

composition, stromal architecture, and suppressive networks—was comprehensively described by Binnewies and colleagues, framing "hot," inflamed tumors as more ICI-responsive and "cold" or immune-excluded tumors as resistant [4].

Contemporary review syntheses across tumor types underscore that immunotherapy has evolved from "a drug class" into a treatment platform—combined with chemotherapy, anti-angiogenic therapy, radiation, targeted therapies, cellular therapy, and novel checkpoints to broaden efficacy [5-7]. This review integrates biologic rationale with clinical evidence, focusing on recent practice-changing advances and the next phase of immuno-oncology.

2. Biological Rationale: From Checkpoints to Systems Immunology

2.1. The PD-1/PD-L1 and CTLA-4 Axes in T-cell Regulation

CTLA-4 primarily modulates early T-cell priming in lymphoid tissues, while PD-1 regulates effector function within peripheral tissues and the tumor bed. When PD-1 binds PD-L1/PD-L2, T-cell signaling is dampened, promoting exhaustion phenotypes and immune escape. Blockade of these inhibitory interactions reactivates effector T-cells but can also break peripheral tolerance, leading to irAEs [1,2].

A practical clinical implication is that different checkpoints map onto different immunologic compartments: CTLA-4 blockade tends to amplify priming and repertoire breadth; PD-1/PD-L1 blockade tends to enhance intratumoral effector function. This compartmentalization supports dual blockade strategies in selected cancers and informs toxicity expectations [8,9].

2.2. The Tumor Immune Microenvironment and the "Hot–Cold" Continuum

The TME comprises tumor cells, immune cells (T cells, macrophages, dendritic cells, neutrophils), stromal fibroblasts, vasculature, and extracellular matrix. Immune-inflamed tumors often exhibit interferon signaling, antigen presentation, and pre-existing CD8+ infiltration, enabling robust ICI activity. By contrast, immune-desert tumors may lack antigenic stimuli or fail T-cell priming; immune-excluded tumors may have T-cells trapped in stroma without tumor penetration [4].

Recent integrative frameworks emphasize multidimensional immune profiling—cellular abundance, spatial localization, and functional states—as essential to predicting ICI benefit. A 2025 multidimensional synthesis of tumor-infiltrating lymphocytes (TILs) highlights how quantity alone is insufficient; spatial patterns and functional exhaustion markers often better correlate with outcomes in the modern immunotherapy era [10].

2.3. Neoantigens And Tumor Mutational Burden: Why Some Tumors Respond Dramatically

Neoantigens arise from somatic mutations that create novel peptides presented by HLA molecules. These non-self-epitopes can be recognized by T cells, enabling immune-mediated tumor control. A 2025 synthesis focusing on neoantigens and tumor mutational burden (TMB) reinforces the mechanistic linkage between mutation-derived antigenicity and ICI responsiveness, while also emphasizing limitations—TMB is a crude surrogate that does not capture antigen clonality, HLA presentation, or immune context [11].

Clinically, TMB has informed pan-tumor treatment concepts, and regulatory frameworks have increasingly reflected biomarker-driven approvals and label indications. A practical reference point for clinicians is the FDA Orange Book as a regulatory record for approved products and indications, which helps track evolving immunotherapy access and combinations [12].

3. Immunotherapy Modalities Beyond Checkpoint Blockade

3.1. Combination Immunotherapy: Principles and Practice

Combination strategies aim to convert "cold" tumors to "hot," enhance antigen release, improve T-cell trafficking, and suppress immunosuppressive networks. Reviews of immunotherapy combinations highlight rationale-based pairing: ICI plus chemotherapy (immunogenic cell death), ICI plus anti-angiogenic therapy (vascular normalization and immune trafficking), dual ICI (breadth + effector restoration), and ICI plus targeted therapy (oncogenic pathway/antigen modulation) [8,13-15].

3.2. Adoptive and Engineered Cellular Therapies in Solid Tumors

Cell-based therapies have transformed hematologic malignancies, but solid tumors pose barriers including antigen heterogeneity, trafficking limitations, and suppressive TME. Comprehensive recent reviews detail evolving platforms: CAR-T, CAR-NK, engineered TCR therapies, and TIL therapy, alongside strategies to improve persistence and penetration [16-19].

A 2025 synthesis on combined ICIs and TIL strategies emphasizes the emerging logic that checkpoint blockade may amplify the function of transferred tumor-reactive lymphocytes, potentially yielding synergistic intratumoral activation [20]. While still maturing clinically, these approaches reflect the "next wave" of immunotherapy—especially for refractory solid tumors.

4. Gastrointestinal Malignancies: From Metastatic Standards to Perioperative Immunotherapy

4.1. Gastric and Gastroesophageal Junction Adenocarcinoma

CheckMate-649 established nivolumab plus chemotherapy as a first-line standard for advanced gastric/GEJ and esophageal adenocarcinoma, improving overall survival compared with chemotherapy alone [21]. Contemporary GI-focused reviews emphasize how PD-L1 enrichment, histologic/biologic heterogeneity, and evolving perioperative trials shape modern management
[5-22].

Perioperative immunotherapy has accelerated recently. MATTERHORN evaluated perioperative durvalumab with FLOT in resectable gastric/GEJ cancers, reflecting a broader paradigm

shift: bringing ICI earlier to potentially improve cure rates [23] KEYNOTE-585 similarly studied perioperative pembrolizumab with chemotherapy, expanding evidence supporting ICI integration in curative-intent settings [24].

4.2. Esophageal Cancer

KEYNOTE-590 demonstrated survival benefit with pembrolizumab plus chemotherapy in advanced esophageal cancer, supporting chemo-immunotherapy as a key first-line approach in appropriate subgroups [25]. Evolving perioperative strategies have also been shaped by comparative analyses and trial syntheses; the ESOPEC trial commentary highlights refinements in multimodality therapy and underscores how perioperative regimen selection is increasingly data-driven [6].

4.3. Colorectal Cancer: MSI-H, Hypermutation, and ctDNA-Enabled Thinking

KEYNOTE-177 established pembrolizumab as first-line therapy for MSI-H metastatic colorectal cancer, with superior progression-free survival compared with chemotherapy and improved tolerability profiles [26]. Beyond MSI, ultra-hypermutated POLE/POLD1 tumors can behave like "immunotherapy-sensitive" disease due to abundant neoantigens. The 2025 report demonstrating ctDNA response and durable benefit after immune checkpoint blockade in POLE-mutant early-onset colon cancer illustrates how molecular phenotype and dynamic ctDNA monitoring can converge to guide precision immunotherapy [7].

4.4. Pancreatic Cancer: Overcoming Cold Biology

Pancreatic ductal adenocarcinoma remains among the most immunotherapy-resistant tumors due to low baseline immunogenicity, dense desmoplastic stroma, immune exclusion, and suppressive myeloid networks. Comprehensive pancreatic management reviews emphasize the urgent need for rational combinations—stroma modulation, vaccine/oncolytic priming, radiation synergy, and multi-agent immunotherapy designs—to generate meaningful activity beyond rare MSI-H cases [27].

5. Hepatobiliary Cancers: Anti-Angiogenic Synergy and Molecular Stratification

5.1. Hepatocellular Carcinoma

IMbrave150 changed first-line therapy for unresectable hepatocellular carcinoma by demonstrating improved survival with atezolizumab plus bevacizumab compared with sorafenib [28]. The biological rationale—simultaneously targeting immune suppression and abnormal tumor vasculature—has become a prototype for combination immunotherapy in other tumors as well. The HIMALAYA regimen (durvalumab with a single priming dose of tremelimumab) further reinforced that checkpoint strategies can produce durable benefit when appropriately designed [29].

5.2. Cholangiocarcinoma and Precision Immunotherapy Frameworks

Cholangiocarcinoma is molecularly heterogeneous. A multidisciplinary synthesis on intrahepatic cholangiocarcinoma emphasizes that immunotherapy decision-making should be integrated with molecular testing and targeted therapy planning, moving toward biomarker-informed selection rather than one-size-fits-all approaches [30]. Recent meeting-level updates (ASCO 2025 abstracts) suggest expanding immunotherapy combinations and trial activity in hepatobiliary and GI malignancies, reflecting ongoing innovation even where benefit has historically been modest [31,32].

6. Breast Cancer: Immunotherapy as a Curative-Intent Strategy—and Beyond TNBC

6.1. Early Triple-Negative Breast Cancer (TNBC)

KEYNOTE-522 established pembrolizumab in combination with chemotherapy in the neoadjuvant setting followed by adjuvant pembrolizumab, improving event-free survival and supporting immunotherapy as a component of curative-intent TNBC management [33]. Reviews focused on immunotherapy in breast cancer emphasize that benefit is context-dependent, shaped by tumor biology, PD-L1/TIL landscape, and optimal integration with chemotherapy backbones [34].

6.2. Hormone Receptor–Positive Disease: Signals and Outliers

While ER+/HER2− breast cancer has typically been less responsive to checkpoint blockade, case-level evidence of exceptional responses can be biologically instructive. The reported exceptional response to pembrolizumab in metastatic ER+/HER2− breast cancer with liver metastases challenges assumptions and highlights that immune responsiveness may emerge in selected contexts—through tumor mutational landscapes, microenvironmental features, or prior therapy–induced immunogenic shifts [35].

7. Renal Cell Carcinoma: ICI Backbones, Sequencing, and Adjuvant Benefit

RCC has become a flagship for immunotherapy combinations. CheckMate-214 established nivolumab plus ipilimumab as a standard for metastatic RCC with durable overall survival benefit [36]. KEYNOTE-426 showed that pembrolizumab plus axitinib improves outcomes relative to sunitinib, cementing ICI plus VEGF-targeting therapy as a major strategy [37]. A contemporary RCC-focused review emphasizes the central clinical questions now: sequencing, resistance patterns, patient selection, and the optimal use of dual ICI versus ICI/VEGF combinations [38]. Importantly, immunotherapy has moved into the adjuvant setting. KEYNOTE-564 demonstrated overall survival benefit with adjuvant pembrolizumab after nephrectomy in high-risk resected RCC [39].

8. Lung Cancer and Head & Neck Cancer: The Perioperative Revolution

8.1. Resectable NSCLC

Perioperative immunotherapy has become one of the most rapidly evolving domains in thoracic oncology. Neoadjuvant nivolumab plus chemotherapy in CheckMate-816 improved pathologic complete response and event-free survival, demonstrating that immune priming in the presence of an intact tumor can translate into meaningful clinical benefit [40]. KEYNOTE-671 evaluated perioperative pembrolizumab plus chemotherapy, while AEGEAN

studied perioperative durvalumab plus chemotherapy [41,42].

8.2. Head and Neck Squamous Cell Carcinoma (HNSCC)

HNSCC is immunogenic in many cases, and checkpoint blockade has become embedded in advanced disease management. Recent evidence supporting neoadjuvant and adjuvant pembrolizumab in resectable HNSCC (KEYNOTE-689) underscores the broader movement of immunotherapy into earlier disease stages in multiple tumor types [43].

9. Gynecologic Malignancies: Chemo-Immunotherapy Becomes Foundational

In endometrial cancer, randomized trials have rapidly changed practice. RUBY demonstrated benefit with dostarlimab plus chemotherapy in advanced or recurrent settings [44]. NRG-GY018 established pembrolizumab plus chemotherapy as another effective approach, with continued updates refining how molecular subtypes (e.g., dMMR vs pMMR) influence magnitude of benefit [45]. In locally advanced cervical cancer, pembrolizumab plus chemoradiotherapy improved outcomes, representing an important proof-of-concept for combining immunotherapy with definitive local therapy [46].

10. Biomarkers and Monitoring: From Enrichment to True Prediction

10.1. PD-L1, MSI/dMMR, and Beyond

Current clinical practice uses several biomarker classes:

- **PD-L1:** widely used but imperfect; varies by assay, scoring, and tumor type; often enriches rather than predicts [25,34].
- **MSI/dMMR:** one of the most robust predictors of ICI response across tumors, exemplified by MSI-H CRC outcomes in KEYNOTE-177 [26].
- **TMB/neoantigens:** mechanistically compelling, but clinically noisy; best interpreted alongside immune context and antigen clonality [11].
- **TILs and immune gene signatures:** increasingly important as multidimensional biomarkers integrating spatial and functional properties [10].

10.2. ctDNA as a Dynamic Biomarker

ctDNA offers a real-time window into tumor burden, minimal residual disease, and early response. The POLE-mutant early-onset CRC report showing ctDNA response with ICI illustrates how ctDNA could help distinguish pseudo-progression from true progression, monitor depth of response, and potentially guide treatment duration [7].

10.3. Microbiome Influences

The gut microbiome influences systemic immunity and response to checkpoint blockade. Landmark studies demonstrated associations between microbiome composition and ICI outcomes in epithelial tumors and melanoma, supporting the concept that microbial ecosystems modulate immune tone and therapeutic responsiveness [47,48].

11. Resistance Mechanisms: Primary, Adaptive, and Acquired Failure

Even in highly immunogenic cancers, resistance limits population-level benefit. Primary resistance includes the absence of T-cell priming, immune desert/exclusion, or dominant suppressive myeloid populations [4]. Acquired resistance involves tumor evolution under immune pressure, including antigen loss, interferon signaling defects, and immune escape mutations. The classic NEJM report on acquired resistance to PD-1 blockade in melanoma describes mutations that disrupt interferon response and antigen presentation, providing mechanistic grounding for resistance management strategies [49].

12. Immune-Related Toxicities: Safety as a Core Competency

ICIs can cause inflammatory toxicities involving dermatologic, gastrointestinal, hepatic, endocrine, pulmonary, neurologic, and renal systems. Kidney injury is a clinically important toxicity domain. A clinicopathologic series defined features of ICI-associated acute kidney injury and underscored the importance of recognition and appropriate immunosuppression [50]. Case-level reports continue to provide granular insights into management, such as pembrolizumab-induced acute interstitial nephritis [51]. Endocrine toxicities are also common; thyroid dysfunction, in particular, may require careful evaluation and longitudinal management [52].

13. Future Directions: What Comes Next

13.1. Next-generation checkpoints and Rational Combinations

Expanding beyond PD-1/CTLA-4 is a major frontier. Contemporary analyses emphasize next-generation checkpoints, optimal sequence design, and strategies to balance efficacy with toxicity [53]. Reviews of “next-generation immunotherapy” highlight the convergence of biomarkers, novel targets, and combination principles including radiotherapy and targeted therapy [54].

13.2. Cellular Therapy for Solid Tumors: Accelerating Translation

Engineered immune cell therapies are rapidly advancing, with innovations aimed at persistence and penetration [16]. Multi-review syntheses in 2023–2025 outline an expanding toolkit: TCR-engineered products, CAR platforms, armored cells, and combinatorial antigen targeting [17-19].

13.3. Precision Immunotherapy: Integrated Biom

The next phase is about the right immunotherapy, for the right patient, at the right time. Molecular profiling enables selection of sensitive subgroups and rational combinations [30,22]. Innovation in single-cell and spatial biology, along with AI-enabled signature discovery, is expected to produce better predictive biomarkers [4,10,54].

13.4. Perioperative Immunotherapy: Redefining Cure Paradigms

Neoadjuvant and perioperative immunotherapy continue to expand across tumors, supported by both mechanistic rationale and large randomized trials [23,24,40-42,55,56]. These strategies

may ultimately alter recurrence patterns and redefine long-term survivorship.

14. Conclusion

Immunotherapy has evolved into a foundational modality in solid tumor oncology, with immune checkpoint blockade transforming outcomes across multiple malignancies and expanding rapidly into perioperative and curative-intent contexts. The field's current challenges—resistance, biomarker imperfections, and irAE management—are now matched by equally rapid innovation: rational combinations, microbiome-directed strategies, ctDNA-guided monitoring, and next-generation cellular therapies. Continued progress will require integrated precision approaches that unify tumor genomics, immune context, dynamic biomarkers, and toxicity-aware clinical decision-making so that durable benefit becomes the rule rather than the exception [57,58].

Tables

Tumor Type	Trial	Regimen	Key Outcome / Clinical Impact
Gastric / GEJ adenocarcinoma (advanced)	CheckMate-649 [17]	Nivolumab + chemotherapy [17]	Overall survival (OS) benefit; established first-line chemo-immunotherapy [17]
Gastric / GEJ (resectable, perioperative)	MATTERHORN [23]	Durvalumab + FLOT [23]	Supports integration of perioperative immunotherapy in curative settings [23]
Gastric / GEJ (resectable, perioperative)	KEYNOTE-585 [24]	Pembrolizumab + chemotherapy [24]	Reinforces perioperative ICI strategy movement into curative settings [24]
Esophageal cancer (advanced)	KEYNOTE-590 [18]	Pembrolizumab + chemotherapy [18]	OS benefit; supports chemo-immunotherapy as first-line approach [18]
Esophageal adenocarcinoma (perioperative)	ESOPEC [7]	Multimodality perioperative strategy refinement [7]	Refines perioperative treatment sequencing and selection [7]
Colorectal cancer (MSI-H, metastatic)	KEYNOTE-177 [19]	Pembrolizumab [19]	PFS benefit; established first-line ICI standard for MSI-H $_{mCRC}$ [19]
Colorectal cancer (POLE-mutated)	Case evidence (ctDNA) [6]	ICI with ctDNA monitoring [6]	Demonstrated ctDNA clearance and durable response [6]
Hepatocellular carcinoma (unresectable)	IMbrave150 [20]	Atezolizumab + bevacizumab [20]	OS benefit; established synergy of ICI + anti-VEGF [20]
Hepatocellular carcinoma (unresectable)	HIMALAYA [35]	Durvalumab + tremelimumab [35]	Durable survival benefit; validates priming-dose CTLA-4 [35]
Renal cell carcinoma (metastatic)	CheckMate-214 [21]	Nivolumab + ipilimumab [21]	OS benefit; established dual ICI standard in risk groups [21]
Renal cell carcinoma (adjuvant)	KEYNOTE-564 [40]	Pembrolizumab (post-nephrectomy) [40]	OS benefit; supports adjuvant ICI in high-risk resected RCC [40]
Triple-negative breast cancer (early)	KEYNOTE-522 [34]	Neoadjuvant + adjuvant pembrolizumab [34]	Improved EFS/OS; moved ICI into curative-intent TNBC [34]
Resectable NSCLC (neoadjuvant)	CheckMate-816 [30]	Nivolumab + chemotherapy [30]	Improved pathologic response and event-free survival [30]
Resectable NSCLC (perioperative)	KEYNOTE-671 [28]	Perioperative pembrolizumab + chemotherapy [28]	Improved EFS; solidifies perioperative ICI paradigm [28]
Resectable HNSCC	KEYNOTE-689 [31]	Neoadjuvant + adjuvant pembrolizumab [31]	Demonstrated benefit; expands perioperative ICI concept [31]
Endometrial cancer (advanced)	$_{RUBY}$ [37]	Dostarlimab + chemotherapy [37]	Survival benefit; established chemo-immunotherapy standard [37]
Cervical cancer (locally advanced)	Pembrolizumab $_{+ CRT}$ [39]	Pembrolizumab + chemoradiotherapy [39]	Improved survival; integrates ICI into definitive setting [39]

Table 1: Key Immunotherapy Trials Across Solid Malignancies

Biomarker / Modulator	Tumor Types Where Most Relevant	Clinical Utility	Key Supporting Evidence
MSI-H / dMMR	CRC, gastric, endometrial, pan-tumor	Strong predictor; enables first-line ICI in MSI-H mCRC	KEYNOTE-177 [19]; biomarker framework reviews [49]
TMB / Neoantigens	Pan-tumor (context-dependent)	Surrogate of immunogenicity; predictive but imperfect	Neoantigen/TMB synthesis [11]; biomarker review [49]
POLE / POLD1 mutations	CRC (esp. early-onset), endometrial	Ultra-hypermutated phenotype; potential for dramatic benefit	POLE ctDNA report [6]; neoantigen synthesis [11]
PD-L1 expression	NSCLC, HNSCC, gastric/GEJ, others	Enrichment biomarker (not universally predictive)	Biomarker review [49]; KEYNOTE-590 [18]
TILs / spatial contexture	Breast, melanoma, many solid tumors	Prognostic and increasingly predictive via spatial analysis	TIL multidimensional review [10]
ctDNA dynamics	Pan-tumor (emerging)	Response monitoring, MRD risk stratification	POLE ctDNA response report [6]
Gut microbiome	Pan-tumor (modulator)	Modulates ICI efficacy; potential target	Routy et al. [50]; Gopalakrishnan et al. [51]
Interferon signaling	Pan-tumor	Mechanistic determinant of acquired resistance	Zaretsky et al. [52]
TME phenotype ("hot vs cold")	Pan-tumor	Framework for combination approaches	Binnewies et al. [4]

Table 2: Biomarkers Predicting Immunotherapy Response or Modulating Outcomes

Figures

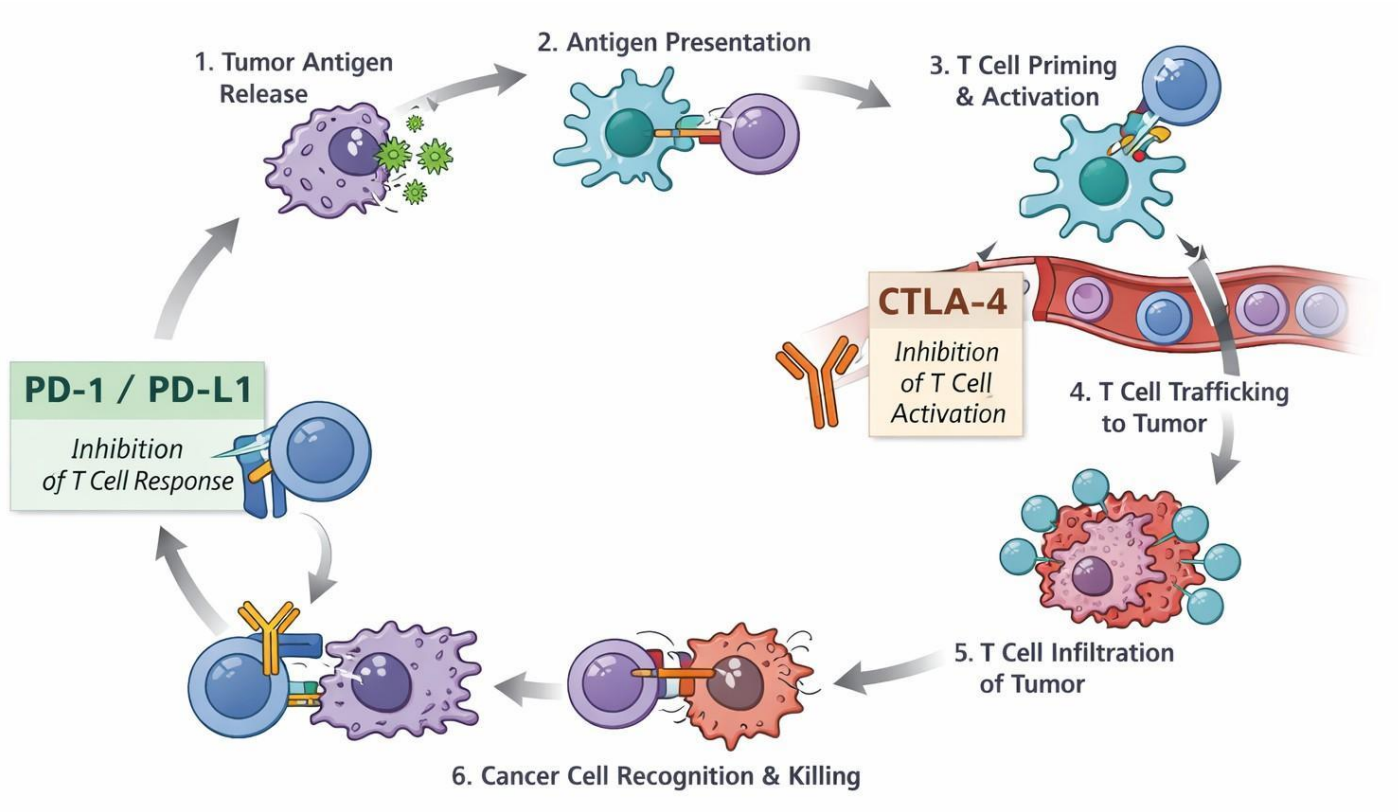

Figure 1: The Cancer-Immunity Cycle and Checkpoint Blockade Targets

This figure illustrates the cancer-immunity cycle, depicting the sequential steps required for effective antitumor immune responses, from tumor antigen release and presentation to T-cell priming, trafficking, tumor infiltration, recognition, and cancer cell killing. CTLA-4 primarily regulates the early priming phase in lymphoid tissues by inhibiting T-cell activation. In contrast, the PD-1/PD-L1 pathway suppresses effector T-cell function within the tumor microenvironment. Immune checkpoint inhibitors restore antitumor immunity by blocking CTLA-4 and PD-1/PD-L1 at their respective stages. This reactivation enables sustained immune-mediated tumor control across multiple solid malignancies.

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