

REVIEW ARTICLE

Understanding the relationship between germ layer origin and cancer therapy response: An analysis and exploratory synthesis

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Abstract

Embryonic germ layer origin fundamentally shapes cancer therapy response patterns, with mesoderm-derived malignancies showing responsiveness to cellular immunotherapy, endoderm-derived epithelial cancers demonstrating sensitivity to protein signaling inhibitors, and ectoderm-derived tumors exhibiting immunogenicity enabling breakthrough responses to checkpoint blockade and mRNA vaccine strategies. To investigate these patterns, we conducted a systematic review, using a guided review method and large language learning models, following the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 guidelines, and searched PubMed, Embase, and Web of Science through October 2025. Evidence synthesis incorporated National Comprehensive Cancer Network Clinical Practice Guidelines, American Society of Clinical Oncology publications, American Cancer Society statistics, and landmark Phase 3 and Phase 4 clinical trials. Given extreme clinical heterogeneity, we performed narrative synthesis with megatrend analysis, employing triple-checking verification methodology of all clinical outcome data using independent search strategies, with explicit documentation of large language model-assisted abstract screening followed by an exclusive human reviewer completion of eligibility assessment, data extraction, and synthesis. Three major megatrends emerged from our analysis: mesoderm-derived hematologic malignancies achieved relevant response rates of 82–97% with chimeric antigen receptor T-cell therapies across multiple pivotal trials; endoderm-derived adenocarcinomas demonstrated vulnerability to targeted therapies, with median overall survival extending to 19–47 months with matched protein pathway inhibitors; and ectoderm-derived melanoma showed immune control with checkpoint blockade achieving approximately 34% 10-year overall survival and 49% risk reduction with personalized mRNA neoantigen vaccines. These findings suggest that embryonic lineage provides a potentially valuable exploratory context for understanding therapeutic response patterns, complementing molecular biomarker-driven precision oncology to guide treatment selection, trial design, and drug development prioritization.

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1. Introduction

1.1. The developmental blueprint of cancer

The relationship between cancer and development represents one of oncology's most profound conceptual connections.^{1,2} During embryonic gastrulation, the specification of three primary germ layers establishes the architectural foundation for all subsequent tissue formation. This trilaminar organization is not merely transient embryonic anatomy but rather represents fundamental cellular commitments that persist throughout organismal life and can be reactivated in malignancy.³

The Cancer Genome Atlas Pan-Cancer Atlas initiative provided compelling support for the cell of origin paradigm through comprehensive molecular characterization of over 20,000 tumors.⁴ When researchers performed unsupervised clustering using integrated data, tumors predominantly grouped by histology and tissue type rather than by shared oncogenic driver mutations, demonstrating that developmental lineage often suggests the importance of tumor core identity as with subsequently acquired somatic mutations.⁴

1.2. Rationale for a germ layer framework

The differential success of modern therapeutic modalities across cancer types, coupled with the established primacy of developmental lineage in defining tumor identity, raises a compelling hypothesis: can the fundamental divisions of embryonic germ layers provide a unifying framework for understanding therapeutic response patterns? This systematic narrative review synthesizes contemporary evidence to explore these relationships, proposing that mesoderm-derived cancers exhibit responsiveness to cellular immunotherapies, endoderm-derived cancers demonstrate inherent vulnerabilities to protein signaling pathway inhibition, and ectoderm-derived cancers show particular promise with nucleic acid-based interventions and immunomodulation.

2. Methods

2.1. Search strategy and verification methodology

We conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 guidelines.⁵ A comprehensive literature search was performed across PubMed/MEDLINE, Embase, and Web of Science Core Collection from database inception through October 2025.

During initial screening of 4,542 unique records, advanced artificial intelligence tools assisted with

high-volume abstract review to prioritize potentially relevant records based on predefined inclusion criteria. The large language model prompts employed were: "identify clinical trials and reviews examining cancer therapy response by tissue origin, germ layer, or developmental lineage. Flag studies reporting objective response rates, progression-free survival, or overall survival for cellular immunotherapy, targeted protein inhibitors, or nucleic acid-based therapies." This preliminary screening generated candidate articles for human review. However, to ensure rigor and accuracy, all subsequent stages, including final eligibility assessment, critical appraisal, data extraction, and synthesis, were conducted exclusively by a human reviewer. Clinical trial data were triple-checked using three independent verification strategies: cross-referencing ClinicalTrials.gov registries with primary journal publications, confirming efficacy parameters across conference presentations and regulatory documents, and validating statistics through manufacturer prescribing information where applicable.

2.2. Germ layer classification and data extraction

Major cancer types were systematically classified according to primary embryonic germ layer origin based on canonical developmental biology principles and insights from large-scale genomic analyses.⁴ Mesoderm-derived cancers included hematologic malignancies, sarcomas, and renal cell carcinoma. Endoderm-derived cancers encompassed adenocarcinomas of the lung, gastrointestinal tract, liver, and pancreas. Ectoderm-derived cancers included melanoma, glioblastoma, squamous cell carcinomas, and breast cancer.

We extracted data identifying therapeutic response patterns corresponding to three predefined modality classes: cellular immunotherapy, protein-targeted agents, and nucleic acid-based interventions. Given extreme clinical and methodological heterogeneity, formal meta-analysis was deemed inappropriate. We therefore performed rigorous narrative synthesis, allowing detailed exploration of relationships between germ layer origin and therapy response.⁶

2.3. Quality assessment

Evidence quality was evaluated using principles derived from the Grading of Recommendations Assessment, Development, and Evaluation methodology. We assessed study design quality, consistency of findings across multiple investigations, directness of evidence, and risk of bias within landmark trials using the Cochrane Risk of Bias 2 tool for randomized studies and ROBINS-I for non-randomized investigations.⁷

3. Megatrend I: Mesoderm-derived malignancies and cellular immunotherapy synergy

3.1. Unprecedented efficacy in hematologic malignancies

The analysis provides robust support for the sensitivity of mesoderm-derived hematologic malignancies to cellular immunotherapies.^{8,9} Landmark chimeric antigen receptor T-cell therapy trials have produced unprecedented efficacy, establishing new treatment paradigms.^{8,10}

In the pivotal ELIANA trial, tisagenlecleucel targeting CD19 induced overall remission rates of 81% in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia, with sustained responses at 3-year follow-up.^{11,12} The initial analysis demonstrated that among 75 infused patients, 61 achieved complete remission or complete remission with incomplete hematologic recovery within 3 months, with all responders achieving minimal residual disease negativity by flow cytometry.¹¹ At median follow-up of 38.8 months, event-free survival reached 44% and overall survival reached 63% at 3 years, with most events occurring within the first 2 years.¹² These outcomes in heavily pretreated pediatric patients with poor prognosis represented a transformative advance, leading to the Food and Drug Administration approval and incorporation into National Comprehensive Cancer Network Acute Lymphoblastic Leukemia Guidelines Version 2.2024 as a preferred option for relapsed or refractory disease.^{10,13}

The ZUMA-1 trial of axicabtagene ciloleucel in refractory large B-cell lymphoma reported objective response rates of 82% with complete response rates of 58%, demonstrating curative potential in heavily pretreated patients.¹⁴ Five-year follow-up data confirmed durability, with 43% of patients remaining progression-free and 42% alive at 5 years post-infusion, supporting curative potential.¹⁵ The ZUMA-7 phase 3 trial elevated axicabtagene ciloleucel to second-line therapy by demonstrating superior overall survival compared to standard care in patients with early relapsed large B-cell lymphoma, fundamentally changing treatment paradigms.^{15,16} Current National Comprehensive Cancer Network B-Cell Lymphomas Guidelines Version 3.2025 incorporate chimeric antigen receptor T-cell therapy as preferred options for diffuse large B-cell lymphoma in second-line and subsequent settings based on this evidence.^{8,17}

In multiple myeloma, the CARTITUDE-1 trial results for ciltacabtagene autoleucel targeting B-cell maturation antigen demonstrated remarkable 97.9% overall response rates with 82.5% stringent complete responses in patients who had exhausted multiple prior therapy lines.^{18,19} At median follow-up of 27.7 months, median duration of

response was not reached, and median overall survival exceeded 41.9 months.¹⁹ Long-term follow-up at a median of 61.3 months revealed that one-third of patients remained alive and progression-free for at least 5 years after a single infusion, with all assessed patients maintaining minimal residual disease negativity and positron emission tomography-computed tomography negativity.²⁰ The phase 3 CARTITUDE-4 trial definitively established ciltacabtagene autoleucel superiority over standard care in lenalidomide-refractory multiple myeloma with one to three prior lines, demonstrating significantly prolonged progression-free survival.²¹ National Comprehensive Cancer Network Multiple Myeloma Guidelines Version 2.2026 now include chimeric antigen receptor T-cell therapy and bispecific antibodies as preferred options for relapsed or refractory disease after appropriate prior therapies, reflecting the transformative impact of cellular immunotherapy.⁹

The KarMMa trial of idecabtagene vicleucel in relapsed or refractory multiple myeloma achieved a 73% overall response rate with 33% complete response, while the phase 3 KarMMa-3 trial demonstrated significant progression-free survival improvement compared to standard regimens in triple-class-exposed patients.^{22,23} TRANSCEND NHL 001 demonstrated lisocabtagene maraleucel efficacy in large B-cell lymphoma with a 73% objective response rate and 53% complete response in the primary efficacy population.²⁴ The phase 3 TRANSFORM trial established lisocabtagene maraleucel superiority in second-line large B-cell lymphoma with an 80% overall response rate and 54.1% complete response versus 48% and 21%, respectively, with standard salvage therapy.²⁵

American Cancer Society statistics reveal the scale of impact.²⁶ Cancer Facts and Figures 2024 projects 62,770 new leukemia cases with 70% 5-year survival, 8,350 new non-Hodgkin lymphoma cases with 74% 5-year survival, and 35,780 new multiple myeloma cases with 59.8% 5-year survival.²⁶ These survival gains occurred rapidly following approvals of tisagenlecleucel, axicabtagene ciloleucel, and subsequent chimeric antigen receptor products. Childhood acute lymphoblastic leukemia now achieves approximately 90% 5-year survival, while Hodgkin lymphoma reaches 93–95% depending on stage, representing some of the most curable cancer types.²⁷

American Society of Clinical Oncology publications document the cellular immunotherapy revolution in hematologic malignancies.^{28,29} The Journal of Clinical Oncology educational series on chimeric antigen receptor T-cell therapy mechanisms, toxicity management, and clinical applications provides comprehensive guidance for practitioners.^{30,31} Reviews trace development from concept

through regulatory approval, highlighting response rates that exceed 80% in appropriate patient populations.³² The American Society of Hematology Educational Program includes annual updates on cellular therapy advances in multiple myeloma, lymphoma, and leukemia, synthesizing evidence for clinical decision-making.

3.2. Mechanistic basis: Developmental synergy

The superior efficacy of cellular immunotherapy in mesodermal hematologic malignancies reflects fundamental biological and architectural features.³⁰ Circulating malignant cells in blood and bone marrow provide direct physical access for intravenously infused engineered T-cells, circumventing formidable challenges of infiltration into dense, fibrotic, poorly vascularized tumor microenvironments characteristic of many solid tumors.³³ Beyond accessibility, the shared mesodermal origin of T-cells and B-cell targets likely fosters developmental synergy. Both cell types arise from hematopoietic stem cells and operate within identical biological contexts of lymphoid organs and bone marrow, implying the use of common molecular toolkits, including matched adhesion molecules and chemokine receptors guiding trafficking and facilitating cell–cell interactions.³⁰

3.3. Challenges in solid mesodermal tumors

Application of cellular therapies to solid tumors of mesodermal origin has proven more challenging, underscoring significant barriers posed by solid tumor microenvironments even within the same germ layer.³³ In sarcomas, engineered T-cell receptor therapies targeting cancer-testis antigens showed promising signals, with recent approval of afamitresgene autoleucel for MAGE-A4 expressing synovial sarcoma achieving 43% objective response rates in heavily pretreated patients.³⁴

In renal cell carcinoma, the feasibility of isolating and expanding functional tumor-infiltrating lymphocytes has been demonstrated with expanded cells showing reactivity against autologous tumors.³⁵ However, clinical efficacy data remain preliminary.

4. Megatrend II: Endoderm-derived neoplasms and protein signaling dependency

4.1. Precision targeting of oncogenic signaling in epithelial cancers

Cancers arising from endoderm, which forms specialized epithelial linings of the gastrointestinal and respiratory tracts, frequently exhibit profound dependencies on protein signaling pathways essential for their normal epithelial function. Therapies precisely inhibiting these

hijacked pathways have become treatment cornerstones across multiple malignancies.^{36,37}

In lung adenocarcinoma, dependency on epidermal growth factor receptor signaling is highlighted by tyrosine kinase inhibitor success. The FLAURA2 trial demonstrated that first-line osimertinib plus chemotherapy achieved a median progression-free survival of 25.5 months compared with 16.7 months for osimertinib monotherapy in patients with EGFR-mutated non-small cell lung cancer, representing a significant 38% reduction in risk of disease progression or death.³⁸ Updated overall survival analysis with median follow-up of 51.3 months revealed median overall survival of 47.5 months with the combination versus 37.6 months with monotherapy, confirming osimertinib plus chemotherapy as first-line standard of care.³⁹ The FLAURA trial previously established osimertinib superiority over first-generation EGFR tyrosine kinase inhibitors, gefitinib or erlotinib, demonstrating median overall survival of 38.6 months versus 31.8 months and establishing osimertinib as preferred monotherapy.⁴⁰ The ADAURA trial further demonstrated osimertinib's benefit in adjuvant settings for resected early-stage disease, reducing disease-free survival events by 83% compared with placebo.⁴¹ National Comprehensive Cancer Network Non-Small Cell Lung Cancer Guidelines Version 8.2025 incorporate osimertinib prominently across treatment stages, including combination with chemotherapy as preferred first-line for EGFR-mutated advanced disease and adjuvant monotherapy for resected stage IB to IIIA disease.^{17,42}

In gastric cancer, HER2-directed antibody drug conjugates transformed treatment outcomes. The DESTINY-Gastric04 phase 3 trial established trastuzumab deruxtecan as second-line standard of care, demonstrating a median overall survival of 14.7 months compared with 11.4 months for ramucirumab plus paclitaxel in HER2-positive gastric or gastroesophageal junction adenocarcinoma, representing a 30% reduction in death risk.⁴³ The trial enrolled 494 patients with metastatic or unresectable disease that progressed during or after trastuzumab-based first-line therapy. Objective response rate reached 44.3% with trastuzumab deruxtecan versus 29.1% with standard therapy, while disease control rate achieved 91.9% versus 75.9%.⁴³ This success was built upon the DESTINY-Gastric01 phase 2 trial, demonstrating a 51% objective response rate versus 14% with chemotherapy and median overall survival of 12.5 months versus 8.4 months in previously treated patients.⁴⁴ National Comprehensive Cancer Network Gastric Cancer Guidelines Version 3.2025 now include trastuzumab deruxtecan as the preferred option for HER2-positive disease after prior trastuzumab-containing therapy, reflecting the transformative impact of antibody-drug conjugates in endoderm-derived malignancies.^{17,45}

4.2. Convergence of anti-angiogenic and immunotherapeutic strategies

The IMbrave150 trial provides compelling evidence for synergistic combination strategies exploiting multiple biological vulnerabilities of endoderm-derived hepatocellular carcinoma.⁴⁶ This phase 3 study established atezolizumab plus bevacizumab as the first-line standard for unresectable hepatocellular carcinoma, demonstrating superior median overall survival of 19.2 months compared with 13.4 months for sorafenib, with a hazard ratio of 0.58.⁴⁶ Updated analysis with median follow-up of 15.6 months confirmed progression-free survival benefit with a median of 6.8 months versus 4.3 months (hazard ratio = 0.59).⁴⁷ The combination leverages hepatocellular carcinoma's characteristic high vascularity targeted by bevacizumab while addressing immunosuppressive tumor microenvironment through programmed death-ligand 1 (PD-L1) blockade with atezolizumab, exemplifying rational combination design based on lineage-specific biology.⁴⁸ National Comprehensive Cancer Network Hepatocellular Carcinoma Guidelines Version 1.2025 designate atezolizumab-bevacizumab as category 1, the preferred first-line therapy for unresectable disease based on this evidence, fundamentally marking a management paradigm shift from multikinase inhibitor monotherapy.^{17,49}

Beyond these anchors, additional targeted therapies enriched endoderm-derived cancer treatment options. The POLO trial identified vulnerability in pancreatic cancer among patients with germline *BRCA* mutations, where maintenance olaparib extended median progression-free survival to 7.4 months versus 3.8 months with placebo following platinum-based chemotherapy.⁵⁰ National Comprehensive Cancer Network Pancreatic Adenocarcinoma Guidelines Version 2.2025 incorporate olaparib for germline *BRCA*-mutated metastatic disease, representing a precision medicine advancement beyond traditional chemotherapy.^{17,51}

American Cancer Society statistics underscore endoderm-derived cancer burden and treatment impact.²⁶ Cancer Statistics 2024 projects lung cancer as the leading cause of cancer death with 127,070 deaths projected, despite declining incidence due to smoking reduction and screening advances.²⁶ However, 5-year survival for localized non-small cell lung cancer now exceeds 63%, reflecting surgical advances and targeted adjuvant therapy implementation.²⁷ Colorectal cancer incidence is increasing in younger adults even as overall rates decline, with 152,810 new cases projected in 2024.²⁶ Colorectal Cancer Facts and Figures 2023–2025 documents 5-year survival of 91% for localized disease and 73% for regional

disease, emphasizing early detection value.⁵² Gastric cancer affects approximately 26,500 Americans annually with strong ethnic disparities, while pancreatic cancer remains among the most lethal with 66,440 new cases and 51,750 deaths projected, though 5-year survival has improved from 5% to 13% over two decades as targeted therapies emerge.²⁷

American Society of Clinical Oncology publications document targeted therapy evolution in endoderm-derived epithelial cancers.^{53,54} The Journal of Clinical Oncology's "Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer with Driver Alterations" guideline provides comprehensive recommendations for EGFR, ALK, and other oncogene-driven diseases, establishing testing and treatment standards.⁵⁵ Molecular testing guidelines from the College of American Pathologists, International Association for Study of Lung Cancer, and Association for Molecular Pathology detail required biomarker panels for selecting tyrosine kinase inhibitor therapy.⁵⁶ Multiple publications trace efficacy evolution from first-generation erlotinib through third-generation osimertinib, documenting resistance mechanisms and sequential therapy strategies.^{40,57} Reviews of antibody-drug conjugates analyze development from concept through clinical success, with trastuzumab deruxtecan representing a paradigm for payload optimization across HER2-expressing malignancies.⁵⁸ American Society of Clinical Oncology Educational Book chapters on "Precision Medicine in Gastrointestinal Cancers" explore biomarker-guided treatment selection and emerging therapeutic strategies.⁵⁹

4.3. Mechanistic basis for endoderm protein signaling dependency

The mechanistic basis for endoderm-derived cancer dependence on protein signaling likely reflects epithelial origin and specialized functions. Endoderm forms the lining of digestive and respiratory tracts, tissues requiring continuous renewal driven by growth factor gradients. EGFR, HER2, VEGF, and related pathways regulate proliferation, differentiation, and survival in these epithelial compartments.⁶⁰ When these tissues transform into adenocarcinomas, they retain and amplify growth factor dependencies, creating oncogene addiction that precision inhibitors exploit.⁶¹ The clinical success of osimertinib in EGFR-mutant lung cancer, trastuzumab in HER2-positive gastric cancer, bevacizumab in colorectal cancer, and sorafenib plus atezolizumab-bevacizumab in hepatocellular carcinoma demonstrates how understanding germ layer biology guides therapeutic development.^{38,43,46}

5. Megatrend III: Ectoderm-derived neoplasms and immunogenic potential

5.1. Melanoma: Paradigm for checkpoint blockade success

The analysis reveals immunotherapy responsiveness in ectoderm-derived melanoma, establishing this malignancy as an archetypal success story for immune checkpoint blockade.^{62,63} The CheckMate 067 trial fundamentally transformed melanoma treatment by demonstrating unprecedented long-term survival with combination nivolumab plus ipilimumab, achieving a minimum 10-year overall survival of 43% in previously untreated advanced melanoma.⁶³ This landmark study randomized 945 patients to receive nivolumab plus ipilimumab, nivolumab alone, or ipilimumab alone. At 10 years, overall survival rates reached 43%, 36%, and 19%, respectively, with median overall survival of 71.9 months for the combination, 36.9 months for nivolumab, and 19.9 months for ipilimumab.⁶³ Among patients achieving complete response, 96% remained free from progression at 10 years, suggesting potential cure in substantial patient subsets.

The KEYNOTE-006 trial established pembrolizumab superiority over ipilimumab, demonstrating median overall survival of 32.7 months versus 15.9 months, with 10-year overall survival of 34% versus 23%.⁶⁴ Building upon systemic success, the CheckMate 238 trial revolutionized adjuvant therapy for resected high-risk melanoma. Nivolumab demonstrated superior recurrence-free survival compared to ipilimumab, with 7-year recurrence-free survival of 46% versus 39% and distant metastasis-free survival of 54% versus 44%.⁶⁵ The KEYNOTE-054 trial similarly established pembrolizumab efficacy in adjuvant settings, reducing recurrence risk by 35% compared to placebo in resected stage III melanoma.⁶⁶

National Comprehensive Cancer Network Melanoma: Cutaneous Guidelines Version 2.2025 incorporate immune checkpoint inhibitors as preferred options across multiple settings, including first-line therapy for unresectable disease, adjuvant therapy for resected high-risk disease, and neoadjuvant approaches for selected patients.^{17,67} The guidelines recognize combination nivolumab plus ipilimumab as category 1 preferred for BRAF wild-type advanced melanoma based on superior long-term outcomes, while targeted therapy with BRAF plus MEK inhibitors represents alternatives for BRAF-mutant disease requiring rapid response.

5.2. Personalized mRNA cancer vaccines: Emerging frontier

The integration of personalized messenger RNA neoantigen vaccines with checkpoint blockade represents

a transformative advancement leveraging melanoma's high mutational burden. The phase 2b KEYNOTE-942 trial demonstrated that a personalized mRNA-4157 vaccine combined with pembrolizumab reduced recurrence or death risk by 49% compared to pembrolizumab alone in resected high-risk melanoma.⁶⁸ At 3-year follow-up, recurrence-free survival reached 74.8% with the combination versus 55.6% with pembrolizumab monotherapy. The vaccine utilized patient-specific tumor sequencing to identify up to 34 neoantigens encoded in a single mRNA construct, administered as nine doses over approximately 1 year concurrent with standard pembrolizumab.

This approach exploits melanoma's exceptional mutational burden, averaging ten mutations per megabase, among the highest across cancer types.⁶⁹ High mutation rates generate numerous neoantigens recognizable as foreign by the immune system, providing abundant targets for personalized vaccine development. The mRNA platform enables rapid manufacturing of patient-specific vaccines within weeks of tumor sequencing, overcoming traditional peptide vaccine limitations.

5.3. Glioblastoma and squamous cell carcinomas: Expanding immunotherapy horizons

While glioblastoma historically demonstrated immunotherapy resistance, emerging evidence suggests potential breakthroughs. The phase 1 trial of a personalized neoantigen-targeting vaccine combined with pembrolizumab in newly diagnosed MGMT-unmethylated glioblastoma demonstrated median progression-free survival of 7.6 months and median overall survival of 16.8 months, comparing favorably to historical controls.⁷⁰ Dendritic cell vaccines loaded with tumor lysate have shown signals of efficacy, with DCVax-L demonstrating median overall survival of 23.1 months in newly diagnosed glioblastoma patients in a phase 3 trial, though regulatory approval awaits confirmatory studies.⁷¹

Head and neck squamous cell carcinoma, another ectoderm-derived malignancy, demonstrated meaningful checkpoint inhibitor responsiveness. The KEYNOTE-048 trial established pembrolizumab plus chemotherapy as the first-line standard for recurrent or metastatic disease, showing superior overall survival compared to cetuximab with chemotherapy, with a median overall survival of 13.6 months versus 10.4 months in the PD-L1 combined positive score ≥ 1 population.⁷² For PD-L1 combined positive score greater than or equal to 20 tumors, pembrolizumab monotherapy achieved a median overall survival of 14.8 months versus 10.7 months with standard therapy.

National Comprehensive Cancer Network Head and Neck Cancers Guidelines Version 2.2025 incorporate

pembrolizumab-based regimens as preferred first-line options based on PD-L1 expression.

5.4. Breast cancer: Immunotherapy integration in triple-negative subtype

Triple-negative breast cancer, characterized by the absence of estrogen receptor, progesterone receptor, and HER2 expression, demonstrates immunotherapy responsiveness distinct from other breast cancer subtypes. The IMpassion130 trial first demonstrated that adding atezolizumab to nab-paclitaxel improved progression-free survival in PD-L1-positive metastatic triple-negative breast cancer, though subsequent IMpassion131 with paclitaxel failed to confirm benefit.⁷³ The KEYNOTE-355 trial definitively established pembrolizumab plus chemotherapy benefit, demonstrating progression-free survival of 9.7 months versus 5.6 months in PD-L1 combined positive score greater than or equal to 10 tumors.⁷⁴

The KEYNOTE-522 trial revolutionized early-stage triple-negative breast cancer treatment by demonstrating that adding pembrolizumab to neoadjuvant chemotherapy increased pathologic complete response rates from 51.2% to 64.8% and improved event-free survival with a hazard ratio zero point sixty-three.⁷⁵ At 5-year follow-up, event-free survival reached 81.3% with pembrolizumab versus 72.3% with chemotherapy alone. National Comprehensive Cancer Network Breast Cancer Guidelines Version 5.2025 incorporate pembrolizumab plus chemotherapy as preferred neoadjuvant and adjuvant treatment for early-stage triple-negative breast cancer regardless of PD-L1 status.^{17,76}

American Cancer Society statistics highlight the impact of these advances. Melanoma 5-year survival has increased from 82% in 2000 to 93.5% in 2024, with much of this improvement attributable to immunotherapy introduction.²⁶ Among patients with distant metastases, 5-year survival improved from 15% to 32% following checkpoint inhibitor approval. Brain cancer remains challenging with 5-year survival of 32.6% overall, though immunotherapy trials offer hope for improvement.²⁷ Triple-negative breast cancer accounts for 10–15% of breast cancers, with immunotherapy now transforming outcomes for this aggressive subtype.²⁷

5.5. Mechanistic basis: Neural crest and immunogenicity

The exceptional immunotherapy responsiveness of melanoma and other ectoderm-derived cancers reflects unique developmental and molecular features. Melanocytes arise from neural crest cells, a transient embryonic population with remarkable migratory capacity and developmental plasticity.⁷⁷ This neural crest

heritage confers distinctive immunogenic properties, including expression of cancer-testis antigens, neural antigens, and differentiation antigens readily recognized by immune cells.

Melanoma's high mutational burden, driven by ultraviolet radiation exposure, generates abundant neoantigens that serve as immune targets.⁷⁸ The cutaneous location provides natural immune surveillance through skin-resident dendritic cells and T cells. Furthermore, melanoma cells retain the capacity for antigen presentation through MHC class I and II molecules, facilitating direct T cell recognition.

6. Discussion

6.1. Synthesis of germ layer patterns

This systematic narrative review provides compelling evidence that embryonic germ layer origin influences cancer therapeutic response patterns, offering a complementary framework to molecular precision oncology. The observed patterns—mesoderm responsiveness to cellular immunotherapy, endoderm sensitivity to protein pathway inhibition, and ectoderm amenability to checkpoint blockade and mRNA vaccines—reflect fundamental developmental biology principles that seemingly persist in malignant transformation.

The success of CAR-T therapy in hematologic malignancies exemplifies how shared developmental origin facilitates therapeutic efficacy. The circulation of both effector T cells and target B cells within the same anatomical compartments, their shared mesodermal lineage, and matched molecular toolkits for trafficking and interaction create optimal conditions for cellular immunotherapy success. Conversely, solid tumor microenvironment barriers highlight the importance of tissue architecture beyond germ layer origin.

Endoderm-derived adenocarcinomas demonstrate consistent dependencies on growth factor signaling pathways essential for epithelial homeostasis. The clinical success of EGFR inhibitors in lung cancer, HER2-targeted agents in gastric cancer, and anti-angiogenic therapy in hepatocellular carcinoma reflects the exploitation of lineage-specific vulnerabilities. These cancers arise from tissues requiring continuous renewal and regeneration, making them particularly susceptible to targeted pathway disruption.

Ectoderm-derived melanoma's exceptional immunotherapy responsiveness combines multiple favorable features: high mutational burden generating numerous neoantigens, neural crest heritage conferring unique immunogenicity, and cutaneous location enabling immune

surveillance. The success of personalized mRNA vaccines builds upon these advantages, demonstrating how understanding developmental biology can guide novel therapeutic development.

7. Clinical implications and future directions

These findings suggest immediate potential clinical relevance for treatment selection, trial design, and drug development prioritization. For newly diagnosed patients, considering germ layer origin alongside molecular profiling may potentially assist in guiding initial therapeutic approaches. Mesoderm-derived hematologic malignancies may prioritize cellular immunotherapy evaluation, endoderm-derived adenocarcinomas suggest comprehensive molecular profiling for targetable alterations, and ectoderm-derived cancers may merit early immunotherapy consideration.

In clinical trial design, stratification by germ layer origin may reduce heterogeneity and improve power to detect treatment effects. Drug development programs might benefit from prioritizing modalities based on factors including the target cancer's developmental origin, accelerating translation of promising approaches. Combination strategies could exploit multiple germ layer-specific vulnerabilities simultaneously.

Future research potentially warrants investigating mechanisms underlying observed patterns through integrated multi-omics analyses comparing therapeutic responses across germ layers. Prospective trials stratifying by developmental origin could potentially validate this framework's clinical utility. Development of germ layer-specific biomarkers may refine patient selection beyond current molecular markers.

8. Limitations

Several limitations warrant consideration. The extreme heterogeneity across cancer types, treatment modalities, and clinical settings precluded formal meta-analysis, limiting quantitative synthesis. Publication bias toward positive results may overestimate treatment effects. The framework's simplification of complex developmental biology cannot capture all nuances of tumor heterogeneity and evolution.

Importantly, this germ layer framework should complement, not replace, established molecular biomarker-driven approaches. Individual patient factors, tumor molecular profiles, and clinical circumstances must guide treatment decisions. The observed patterns represent population-level trends with substantial individual variation.

9. Conclusion

This systematic narrative review demonstrates that embryonic germ layer origin provides valuable context for understanding cancer therapeutic response patterns. Mesoderm-derived hematologic malignancies show responsiveness to cellular immunotherapy, achieving complete response rates exceeding 80% with CAR-T therapy. Endoderm-derived epithelial cancers demonstrate vulnerability to protein signaling inhibitors, with targeted agents extending survival by months to years. Ectoderm-derived cancers exhibit immunogenicity, enabling breakthrough responses to checkpoint blockade and personalized mRNA vaccines.

These patterns reflect fundamental developmental biology principles that persist through malignant transformation. By integrating germ layer considerations with molecular precision oncology, clinicians can potentially optimize treatment selection, researchers can potentially design more effective trials, and drug developers can potentially prioritize promising therapeutic strategies. As cancer medicine advances toward increasingly personalized approaches, understanding the developmental blueprint underlying malignancy offers a potentially valuable framework for therapeutic innovation.

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