Novel Biomarkers and Therapeutic Avenues for Precision Oncology and Effective Treatment Strategies

Md Anisul Islam Khan [1*], Nur A Zannat [2]

Abstract

Cancer remains one of the most significant global health challenges, necessitating continuous innovation in its diagnosis and treatment. This review highlights the paradigm shift in cancer research and therapeutic strategies, focusing on the transformative role of novel biomarkers and precision oncology. Advances in high-throughput omics technologies and an enhanced understanding of molecular processes have led to the discovery of diverse cancer biomarkers. These biomarkers transcend traditional histopathological classifications, incorporating genetic, epigenetic, and proteomic insights to refine our understanding of cancer heterogeneity. By leveraging these tumor-specific signatures, oncologists can implement highly personalized diagnostic and therapeutic approaches, enabling early detection, precise prognostication, and the identification of previously unrecognized therapeutic targets. This review also explores the groundbreaking therapeutic modalities that have emerged alongside these biomarkers. Immunotherapies, including immune checkpoint inhibitors and CAR-T cell therapies, have revolutionized cancer treatment by utilizing the immune system to selectively target malignancies. Similarly, gene-editing technologies such as CRISPR-Cas9 offer unprecedented potential for correcting genetic aberrations that drive cancer progression. These innovative strategies not only improve treatment efficacy but also minimize the adverse effects often associated with conventional chemotherapy and radiation therapy. In conclusion, the integration of novel biomarkers with precision oncology is redefining cancer management. Through personalized diagnostics and cutting-edge therapies, oncologists can deliver tailored treatment plans that enhance patient outcomes and quality of life. This review underscores the transformative potential of these advancements, offering a hopeful outlook toward a future where cancer is effectively controlled and, in some cases, even cured.

Keywords: Precision Oncology, Novel Biomarker,. Cancer Targets, Therapeutic Avenues,. Personalized Treatment

Significance | Precision oncology, driven by novel biomarkers and advanced therapies, promises personalized treatments, improved outcomes, and potential cancer eradication.

*Correspondence. Md Anisul Islam Khan , Catalent Pharma Solutions, 2125 Ambassador Dr, Windsor, Ontario N9C 3R5, Canada.
Email: anisulshuvo.pharm@gmail.com

Editor Md Shamsuddin Sultan Khan And accepted by the Editorial Board November 16, 2024 (received for review September 02, 2024)

Introduction

Cancer remains one of the most significant threats to human health and continues to pose challenges for medical research. Often referred to as the "Pathology of the Century," cancer is widely regarded as a global epidemic, symbolizing the complexities of modern disease. Scholars such as Roy Porter and Siddhartha Mukherjee have aptly described cancer as “the contemporary illness at its best” and “the defining example of a contemporary product,” respectively (Arnold-Forster & Mukherjee, 2011). These perspectives underscore the sharp rise in cancer incidence and mortality observed since the late 18th century, culminating in its

Author Affiliation.
[1] Catalent Pharma Solutions, 2125 Ambassador Dr, Windsor, Ontario N9C 3R5, Canada.
[2] Medical Biotechnology, University of Windsor, Ontario, Canada.

Please Cite This:
Khan, M. A. I., Zannat, N. A. (2024). "Novel Biomarkers and Therapeutic Avenues for Precision Oncology and Effective Treatment Strategies", Journal of Angiotherapy, 8(11),1-8,10065

position as the second leading cause of death globally (Ferlay et al., 2015). In 2015 alone, cancer was responsible for 8.7 million deaths worldwide, while new cases reached 17.5 million (GBD Collaborators on Mortality Causes of Death, 2016). Despite advancements in diagnostics, therapeutics, and interventional techniques, the global cancer burden continues to grow, driven by population expansion and increasing life expectancy. Between 2005 and 2015, the number of new cancer cases surged by approximately 33% (Global Burden of Disease: Cancer, 2018). Paradoxically, while incidence rates have climbed, mortality rates in some regions have declined, reflecting the complex interplay between early detection, therapeutic innovation, and persistent challenges in addressing cancer's heterogeneity.

A pivotal development in cancer treatment has been the emergence of precision oncology, a revolutionary approach that tailors therapeutic strategies to the genetic and molecular profiles of individual tumors (Collins & Varmus, 2015). This paradigm shift addresses the shortcomings of conventional cancer treatments, such as cytotoxic chemotherapy, which—despite its initial success—has been plagued by toxicity, drug resistance, and limited specificity (Chabner & Roberts, 2005).

Over the past two decades, advances in biotechnology have led to novel therapeutic strategies that have significantly improved patient outcomes. Monoclonal antibodies and immunotherapeutic agents, such as checkpoint inhibitors, have laid the groundwork for personalized medicine, offering enhanced efficacy with reduced safety concerns (Scott et al., 2012). Similarly, gene therapy approaches, exemplified by Yescarta and Kymriah, and CAR-T cell therapies have demonstrated transformative potential in targeting cancer at its molecular core (Vile et al., 2000).

The integration of biomarkers into therapeutic protocols represents another key advancement. Biomarkers facilitate early cancer detection, monitor disease progression, and guide treatment selection, thereby enhancing therapeutic precision. Additionally, combination protocols—blending various drugs and treatment modalities—are increasingly being explored in clinical trials, aiming to optimize efficacy and overcome pharmacological resistance (Hu et al., 2010).

Despite these advances, precision oncology faces challenges, including the high cost of therapies, accessibility disparities, and the need for more robust biomarkers. Nonetheless, it holds immense promise for improving cancer outcomes by aligning treatments with the unique molecular landscapes of individual tumors. This review seeks to critically examine the potential and limitations of precision oncology, offering a balanced perspective on its role in revolutionizing cancer care.

2. Case Study: Transforming Cancer Care Through Precision Medicine

Chen's story exemplifies the transformative potential of precision medicine in cancer care. His journey from diagnosis to hopeful recovery underscores how individualized treatment, rooted in genetic profiling, can dramatically improve outcomes.

At 55 years old, Chen, a non-smoker with no family history of lung cancer, was diagnosed with early-stage lung cancer through a high-risk screening program. A liquid biopsy detected trace amounts of tumor DNA in his blood, revealing a specific genetic mutation associated with lung cancer. Subsequent imaging confirmed a small tumor in his right lung, which was successfully removed via surgery. Post-operative genetic testing reaffirmed the mutation linked to his cancer, guiding his oncologist to recommend targeted therapy with Tagrisso (osimertinib).

Tagrisso, a medication designed to inhibit the activity of specific genetic mutations, significantly reduces tumor growth and the risk of recurrence. Chen's treatment was informed by the ADAURA trial, which demonstrated an 80% reduction in the likelihood of cancer recurrence or death in early-stage lung cancer patients treated with Tagrisso compared to a placebo. Chen adhered to a daily regimen of Tagrisso for three years, monitored regularly through blood tests to detect residual or recurring tumor DNA.

Throughout his treatment, Chen experienced mild side effects, such as a rash and diarrhea, but no detectable signs of disease recurrence. This consistent absence of tumor DNA gave him hope and confidence in his future. He resumed his normal activities, including work, travel, and time with loved ones, highlighting how precision medicine can enhance not only survival but also quality of life (Harb, 2020).

Chen's case demonstrates the power of precision oncology, a groundbreaking approach that tailors treatment to the genetic and molecular characteristics of an individual's cancer.

3. Genomic and Other Biomarkers

The foundation of precision medicine lies in genomic studies, but recent advances indicate that RNA and protein profiles are also critical in mediating biological effects. Proteins, as signaling effectors, play an essential role in cancer progression and treatment response. However, technical challenges have made genomic-based patient-drug matching more successful than protein-based methods (Lee et al., 2016). Despite current limitations, combining protein and transcriptomic tests with genomics may provide more comprehensive insights into disease mechanisms.

Immunological signature panels incorporating DNA, RNA, and protein data have gained increasing therapeutic relevance in recent years (Nesline et al., 2019). These multi-omic approaches enhance precision medicine by enabling oncologists to predict responses to immunotherapies and other targeted treatments.

3.1 Advances in Genomics

The rise of next-generation sequencing (NGS) technologies has revolutionized precision oncology, with significant progress in standardizing sequencing methods, variant annotation, and data interpretation. Guidelines for NGS panel validation (Jennings et al., 2017) and the clinical reporting of genomic variants (Duncavage et al., 2017) have bolstered the reliability of genomic diagnostics. Although whole-genome sequencing is not yet routine in clinical settings, the FDA has approved NGS panels that test hundreds of genes, offering valuable insights for personalized treatment (FDA, 2017).

Chen's story and the broader advancements in biomarkers and genomics illustrate how precision medicine is reshaping cancer care, providing a path toward more effective, tailored treatments that improve patient outcomes.

4. Blood-Derived Cell-Free DNA Analysis

Clinical-grade circulating tumor DNA (ctDNA) analysis, a non-invasive technique, is gaining prominence in cancer therapy selection and monitoring of tumor dynamics. This method leverages ctDNA, which reflects tumor heterogeneity as it originates from various metastatic lesions and leaks into the bloodstream. The use of ctDNA provides insights into subclone dynamics during treatment (Chabon & Jack, 2018).

However, discrepancies between ctDNA testing and tumor tissue genotyping results have been observed (Merker et al., 2018). These inconsistencies may stem from technical limitations but could also be attributed to biological factors. For example, ctDNA captures DNA shed from multiple tumor sites, while tumor next-generation sequencing (NGS) analyzes a small, localized biopsy. Moreover, ctDNA levels are linked to overall tumor burden, allowing its detection even in minimal quantities.

4.1 Blood-Derived Circulating Tumor Cell (CTC) Analysis

Circulating tumor cells (CTCs), epithelial-derived cells present in the bloodstream, have been associated with poorer survival outcomes in multiple cancer types (Ellis et al., 2004). For example, a multicenter prospective study in metastatic breast cancer revealed that high CTC counts correlated with shorter progression-free survival (PFS) and overall survival (OS) (Ellis et al., 2004).

CTCs also hold potential as biomarkers for immunotherapy and chemotherapy. For instance, repeated CTC analyses enable real-time monitoring of disease progression (Hiltermann et al., 2012). In metastatic castration-resistant prostate cancer, a comparative study of five phase III clinical trials demonstrated that CTCs were more predictive of outcomes than prostate-specific antigen levels (Kheoh et al., 2018).

Despite these promising findings, the integration of CTCs into routine clinical practice remains limited, warranting further research to establish their utility in guiding treatment decisions.

5. Transcriptomics

Transcriptomics, the study of RNA transcripts, is a valuable tool for understanding gene expression and its regulation. High-throughput methods, such as microarrays and RNA sequencing, enable the identification of prognostic and predictive gene expression profiles (Makower et al., 2018). Transcriptomics also provides insights into miRNA regulation of mRNA (Michuda et al., 2019) and assists in determining the tissue of origin in cancers of unknown primary origin.

The WINTHER trial demonstrated the clinical utility of transcriptomics by comparing RNA expression in tumors and adjacent normal tissues, leading to an increased number of patients matched to targeted therapies (Berger et al., 2019). However, significant inter-patient heterogeneity in RNA expression necessitates patient-specific comparisons between tumor and normal tissues.

Despite its potential, transcriptomics faces challenges, including RNA degradation in formalin-fixed tissue samples, complex bioinformatic analysis, and limited reproducibility of results (Kesper et al., 2018). Addressing these issues is essential for broader clinical adoption.

6. Proteomics

Proteomic analysis focuses on the protein composition of tumors and its implications for therapeutic decision-making. Studies using immunohistochemistry and other proteomic assays have identified molecular targets associated with improved progression-free survival (PFS) in refractory metastatic cancer (Hoff et al., 2010).

In clinical settings, proteomic tests are used to identify biomarkers such as hormone receptor expression, HER2 overexpression, and ALK expression, which guide targeted therapies. However, proteomic markers often exhibit weaker correlations with clinical outcomes compared to genomic markers, raising concerns about their reliability (Lee et al., 2016).

A meta-analysis of phase I clinical trials highlighted this disparity, showing a 41% response rate with genetic biomarkers compared to 25% with protein biomarkers ($p = 0.05$) (Lee et al., 2016). Current trials, such as LEEomic (NCT03613220) and BABST-C (NCT03743428), aim to identify proteomic indicators of response or resistance by analyzing tumor tissue and peripheral blood samples.

7. Advancements in Immunotherapy

Immunotherapy has revolutionized cancer treatment by reactivating the immune system's ability to target tumors (Worst et al., 2016). Innovative strategies under investigation include checkpoint inhibitors, oncolytic viruses, modified cytokines, CD3-bispecific antibodies, and adoptive cell therapies (Makker et al., 2019).

These advancements underscore the shift toward personalized and targeted approaches in oncology, aligning with the broader goals of precision medicine. By integrating tools like ctDNA, CTCs, transcriptomics, and proteomics, oncologists can better tailor treatments to individual patients, improving outcomes and quality of life. This comprehensive approach marks a significant step forward in the fight against cancer, offering new hope for patients and redefining the future of cancer care.

8. Checkpoint Blockade

Checkpoint inhibitors have revolutionized cancer immunotherapy, with seven FDA-approved agents: ipilimumab, pembrolizumab, nivolumab, avelumab, cemiplimab, durvalumab, and atezolizumab. These therapies have yielded remarkable responses, including durable complete remissions (CR) in some patients with advanced disease. However, approximately 80% of patients with cancer do not benefit from checkpoint inhibitor therapy, despite its success across various tumor types.

In the precision medicine era, genomic, transcriptomic, and other technologies are employed to identify biomarkers that predict response to immunotherapy. Genetic indicators such as tumor mutational burden (TMB) and microsatellite instability (MSI-H) have shown potential in predicting checkpoint inhibitor efficacy. Mismatch repair deficiencies leading to MSI-H are associated with elevated TMB, PBRM1 alterations, and PDL1 amplification (Wang et al., 2015). High TMB (≥20 mutations/MB) has been linked to significant improvements in progression-free survival (PFS) and overall survival (OS) among checkpoint inhibitor recipients (Bazhenova et al., 2017). In a study of 1638 patients, those with high TMB demonstrated substantial therapeutic benefit compared to patients with low or moderate TMB (Bazhenova et al., 2017).

However, the utility of TMB as a biomarker is contested. Some studies have questioned its predictive value and highlighted the need for additional research (Gadgeel et al., 2019). Current biomarkers remain insufficient to reliably predict immunotherapy response. Emerging strategies, such as incorporating circulating tumor DNA (ctDNA) analysis, and integrating immune, genomic, transcriptomic, and proteomic data from tumor tissues, may enhance biomarker accuracy and utility (Gadgeel et al., 2019).

9. Adoptive Cell Therapy

Adoptive cell therapy (ACT) is a promising patient-specific approach that enhances immune system function to eliminate tumor cells. This method involves the in vitro expansion of immune cells harvested from a patient's blood or tumor tissue, which are then reintroduced into the patient. These cells may be modified to recognize tumor-specific antigens (Schumacher et al., 2002). ACT encompasses therapies such as tumor-infiltrating lymphocyte (TIL) therapy, chimeric antigen receptor (CAR) T-cell therapy, engineered T-cell receptor (TCR) therapy, and natural killer (NK) cell therapy.

9.1 Tumor-Infiltrating Lymphocytes (TILs)

TIL therapy uses T-cells that have naturally migrated into a patient's tumor. After extraction, these autologous cells are expanded and activated before reinfusion. TIL therapy has shown promising results in metastatic melanoma, nasopharyngeal carcinoma, and cervical cancer. For instance, three clinical trials in metastatic melanoma reported objective response rates of 49%, 52%, and 72%, with durable CRs observed in 22% (20 of 93 patients). These benefits were achieved regardless of prior therapies (Sherry et al., 2011). Ongoing clinical trials continue to evaluate TIL therapy in various solid tumors (NCT03645928, NCT03935893, NCT03108495, NCT03083873).

9.2 CAR T-Cells

Chimeric antigen receptor (CAR) T-cell therapy involves genetically engineering a patient's T lymphocytes to recognize antigens expressed on cancer cells. CAR T-cell therapy has demonstrated extraordinary efficacy in hematologic malignancies, with durable CR rates even in patients with refractory disease. The FDA has approved CAR T-cell therapies for relapsed or refractory B-cell precursor acute lymphoblastic leukemia in children and young adults, as well as for relapsed/refractory diffuse large B-cell lymphoma in adults.

While CAR T-cells have achieved success in hematologic cancers, their application to solid tumors remains under investigation (ACTolog, 2016). These efforts highlight the potential of CAR T-cell therapy as an adaptable and potent treatment modality.

Checkpoint blockade and adoptive cell therapies represent transformative advances in cancer immunotherapy. While checkpoint inhibitors have shown efficacy in some patients, the limited utility of biomarkers like TMB underscores the need for more precise predictive tools. Similarly, adoptive cell therapies, including TIL and CAR T-cell treatments, are expanding therapeutic possibilities, particularly in refractory and advanced-stage cancers. Continued innovation and research will be crucial to optimizing these approaches and improving outcomes for a broader patient population.

9.3 TCR Therapy

T-cell receptor (TCR) therapy involves modifying T-cells with retroviruses to incorporate novel TCR transgenes, enabling the cells to target antigens highly expressed on various malignancies (Debets et al., 2010). This approach has been studied in both hematologic and solid tumors (Wunderlich et al., 2006). Current clinical trials focus on evaluating treatment-associated toxicity, binding affinity to tumor antigens, and overall effectiveness, particularly in carefully selected patients with high tumor burdens.

9.4 NK Cell Therapy

Table 1. Examples of Precision Medicine Trials: Design and Outcomes

Trial Name	No. of Patients Screened (N)	Proportion of Patients Matched	Biomarker	Outcomes	Year	First/Last Author(s)
Bisgrove	86	77%	IHC, FISH, microarray	27% of 66 matched patients had a PFS2/PFS1 ratio ≥ 1.3 (95% CI, 17% to 38%; p = 0.007).	2010	Von Hoff D, Penny R
IMPACT, first cohort	1144	15%	PCR-based genomics, 9 genes	Matched vs. unmatched: RR: 27% vs. 5% (p < 0.0001), TTF: median, 5.2 vs. 2.2 months (p < 0.0001), OS: median, 13.4 vs. 9.0 months (p = 0.017).	2012	Tsimberidou A, Kurzrock R
MOSCATO	1035	19%	Targeted NGS (40–75 genes), aCGH, RNAseq	PFS2/PFS1 ratio ≥ 1.3 in 33% (63/193) of patients. Conducted at Institut Gustave Roussy.	2017	Massard C, Soria JC

Natural killer (NK) cells are cytotoxic lymphocytes critical for innate immunity and represent promising tools for cancer therapy. Unlike other immune cell therapies, NK cells do not cause graft-versus-host disease, making them particularly appealing in clinical settings. For instance, recombinant human interleukin-15 combined with haploidentical NK cells has been used successfully in treating relapsed or refractory acute myeloid leukemia (Bachanova et al., 2019). CAR-NK cells, which are genetically engineered to target specific tumor antigens, are currently being evaluated in clinical trials for both hematologic (NCT03056339, NCT00995137) and solid cancers (NCT03656705, NCT03383978).

9.5 Chemotherapy

Chemotherapy remains a cornerstone of cancer treatment, using drugs to destroy cancer cells by interfering with their ability to divide and grow. It can be administered intravenously, orally, or topically, depending on the type and stage of the cancer. While effective, chemotherapy often causes side effects like nausea, fatigue, and hair loss due to its impact on healthy cells. Treatment regimens are tailored to the cancer type, stage, and patient's overall health, and chemotherapy is often integrated into broader cancer treatment plans that may include surgery, radiation therapy, and immunotherapy.

9.6 Personalized Vaccines

The accumulation of somatic mutations in cancer produces cancer-specific neo-epitopes, which are promising targets for cancer vaccines. These neo-epitopes are recognized as foreign substances by autologous T lymphocytes, making them ideal candidates for therapeutic development. While each cancer exhibits unique mutations, only a subset of neo-antigens is commonly shared across malignancies.

Advances in technology are paving the way for rapid genetic mapping, the selection of vaccine targets like neo-epitopes, and the on-demand production of patient-specific vaccines. For cancers with shared epitopes, commercially available vaccines may also become viable options.

Ongoing clinical trials are testing several personalized cancer vaccines (Miller et al., 2017). For example, customized RNA mutanome vaccines were developed for metastatic melanoma using computationally predicted neo-epitopes. Among five patients treated, two exhibited objective responses to the vaccine alone, while a third achieved complete remission when the vaccine was combined with PD-1 blockade therapy (Miller et al., 2017).

In another study, vaccine-induced polyfunctional CD4+ and CD8+ T-cells targeting distinct neo-antigens were assessed in melanoma patients. Four out of six vaccinated patients experienced no recurrence at 25 months post-vaccination (Miller et al., 2017). These promising results highlight the potential of personalized vaccines as a transformative cancer therapy.

TCR and NK cell therapies, chemotherapy, and personalized vaccines each offer unique advantages in the fight against cancer. Advances in precision medicine and immunotherapy are enabling increasingly targeted and effective treatment options. Continued innovation and clinical research will help refine these approaches, ultimately improving outcomes for a broader spectrum of cancer patients.

10. Challenges and Solutions for Optimal Implementation of Precision Medicine

Genomic studies have revealed the complexity and heterogeneity of tumors, demonstrating that traditional clinical research and treatment paradigms often fail to achieve optimal outcomes. Research on precision medicine (Table 1) highlights significant challenges in designing and conducting trials under this new paradigm. In precision medicine studies, the rate at which patients are matched to targeted therapies ranges from 5% to 49%, with a typical range of 15% to 20%.

10.1 Challenges in Precision Medicine Implementation

Several factors contribute to the low patient-matching rates:

Patient Attrition: Patients with advanced disease may deteriorate or die before completing genomic testing and study enrollment.

Limited Gene Panels: Small panels often yield few actionable alterations, limiting therapeutic options.

Delays in Genomic Processing: Time-consuming receipt and interpretation of genomic results hinder timely treatment.

Drug Accessibility: Targeted therapies are often challenging to obtain due to availability and regulatory constraints.

10.2 Variability in Response to Treatment

One major obstacle is the variability in treatment response based on histology and genetic co-alterations. Selected genomic markers, such as MSI-H or NTRK fusions, predict tumor-agnostic responses, whereas others are histology-specific (Kummar et al., 2018). Additionally, the variability and dynamic nature of tumor genomic landscapes complicate precision medicine. Molecular profiling of a single lesion may fail to accurately reflect systemic disease due to disparities between primary and metastatic tumors (Lovely et al., 2016).

10.3 Immunotherapy Challenges

The enthusiasm for immunotherapy has led to numerous patients enrolling in studies without molecular profiling or immune marker assessment. While a subset of patients benefits significantly, most experience disease progression or severe adverse effects. Biomarker optimization is critical to better identify candidates for immunotherapy.

10.4 Real-World Data Integration

Real-world data offers immense potential to enhance precision medicine. Comparing clinical trial outcomes with real-world database insights can validate database information. If findings

align, real-world data could expedite the prediction of new applications for approved therapies. Addressing these challenges through improved biomarker utilization, streamlined genomic testing, and leveraging real-world evidence will enable more effective precision medicine strategies, improving patient outcomes.

11. Conclusion

In conclusion, the field of cancer research and treatment is undergoing a transformative shift, largely driven by the discovery of novel biomarkers and the rise of precision oncology. These advancements promise to fundamentally change how we approach the diagnosis, classification, and treatment of cancer. By tailoring interventions to the unique molecular profiles of individual tumors, we can significantly enhance diagnostic accuracy, refine prognosis predictions, and optimize therapeutic strategies, ultimately improving patient outcomes.

The emergence of groundbreaking therapeutic options, such as immunotherapies and gene therapies, further highlights the potential to offer more effective, targeted treatments with fewer side effects than traditional approaches. These therapies are paving the way for a future where cancer treatment is not only more precise but also less invasive, reducing the overall burden on patients and enhancing their quality of life.

As our understanding of cancer biology deepens and we continue to unravel the genetic and molecular complexities of the disease, the potential for precision oncology becomes even more promising. This personalized approach to cancer care offers new hope for improved survival rates, better quality of life, and, in the long run, the possibility of controlling or even eradicating cancer altogether.

Ultimately, the integration of novel biomarkers and precision oncology is reshaping cancer care, enabling healthcare providers to offer treatments that are as unique as the patients themselves. This paradigm shift brings us closer to overcoming one of the greatest challenges in modern medicine, offering renewed hope for a future where cancer can be managed, if not defeated, on a global scale.

Author contributions

M.A.I.K. conceptualized the study, supervised the research process, and contributed to data analysis and manuscript drafting. N.A.Z. collected and analyzed data, assisted in literature review, and contributed to manuscript writing and revisions. Both authors reviewed and approved the final version of the manuscript.

Acknowledgment

The authors were grateful to their department.

Competing financial interests

The authors have no conflict of interest.

References

A. Drilon, T.W. Laetsch, S. Kummar, et al.Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children N Engl J Med, 378 (2018), pp. 731-739

A.M. Goodman, S. Kato, L. Bazhenova, et al.Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers Mol Cancer Ther, 16 (2017), pp. 2598-2608

ACTolog in Patients With Solid Cancers (ACTolog). 2016. (Accessed 6/24/2019

Arnold-Forster, A. (2016). A pathology of progress? Locating the historiography of cancer. Br. J. Hist. Sci. 49, 627–634

B. Weidenbusch, G.H.S. Richter, M.S. Kesper, et al.Transcriptome based individualized therapy of refractory pediatric sarcomas: feasibility, tolerability and efficacy Oncotarget, 9 (2018), pp. 20747-20760

B.C. Worst, C.M. van Tilburg, G.P. Balasubramanian, et al. Next-generation personalised medicine for high-risk paediatric cancer patients - The INFORM pilot study Eur J Cancer, 65 (2016), pp. 91-101

C.M. Lovly, A.K.S. Salama, R. Salgia Tumor Heterogeneity and Therapeutic Resistance Am Soc Clin Oncol Educ Book (2016), pp. E585-e593

Chabner, B. A., and Roberts, T. G. Jr. (2005). Timeline: chemotherapy and the war on cancer. Nat. Rev. Cancer 5, 65–72

Collins, F. S., & Varmus, H. (2015). A new initiative on precision medicine. New England Journal of Medicine, 372(9), 793-795.

D. Von Hoff, J.J. Stephenson Jr., P. Rosen, et al. Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers J Clin Oncol, 28 (2010), pp. 4877-4883

D.T. Le, J.N. Uram, H. Wang, et al.PD-1 Blockade in Tumors with Mismatch-Repair Deficiency N Engl J Med, 372 (2015), pp. 2509-2520

Dagogo-Jack, A.T. Shaw Tumour heterogeneity and resistance to cancer therapies Nat Rev Clin Oncol, 15 (2018), pp. 81-94

G. Heller, R. McCormack, T. Kheoh, et al.Circulating Tumor Cell Number as a Response Measure of Prolonged Survival for Metastatic Castration-Resistant Prostate Cancer: A Comparison With Prostate-Specific Antigen Across Five Randomized Phase III Clinical Trials J Clin Oncol: Off J Am Soc Clin Oncol, 36 (2018), pp. 572-580

GBD Mortality and Causes of Death Collaborators (2016). Global, regional, and national life expectancy, all-causemortality,and cause-specific mortality for 249causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388, 1459–1544.

Genomic Profiling Tests Cleared by FDA. 2017. (Accessed 7/12/2019, at https://www.cancer.gov/news-events/cancer-currents-blog/2017/genomic-profiling-tests-cancer).

Global Burden of Disease Cancer Collaboration, Fitzmaurice, C., Akinyemiju, T. F., Al Lami, F. H., Alam, T., Alizadeh-Navaei, R., et al. (2018). Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer Groups, 1990 to 2016: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol

Hu, C. M., Aryal, S., Zhang, L. (2010). Nanoparticle-assisted combination therapies for effective cancer treatment. Ther. Deliv. 1, 323–334

J. Michuda, C. Igartua, T. Taxter, J.S. Bell, R. Pelossof, K. White Transcriptome-based cancer type prediction for tumors of unknown origin J Clin Oncol, 37 (2019), p. 3081-

J. Rodon, J.C. Soria, R. Berger, et al.Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial Nat Med, 25 (2019), pp. 751-758

J. Rodon, J.C. Soria, R. Berger, et al.Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial Nat Med, 25 (2019), pp. 751-758

J.A. Sparano, R.J. Gray, D.F. Makower, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer N Engl J Med, 379 (2018), pp. 111-121

J.D. Merker, G.R. Oxnard, C. Compton, et al.Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review Arch Pathol Lab Med (2018)

J.J. Chabon, A.D. Simmons, A.F. Lovejoy, et al.Circulating tumour DNA profiling reveals heterogeneity of EGFR inhibitor resistance mechanisms in lung cancer patients Nat Commun, 7 (2016), p. 11815

K.L. Jhaveri, X.V. Wang, V. Makker, et al. Ado-trastuzumab emtansine (T-DM1) in patients with HER2-amplified tumors excluding breast and gastric/gastroesophageal junction (GEJ) adenocarcinomas: results from the NCI-MATCH trial (EAY131) subprotocol Q Ann Oncol, 30 (2019), pp. 1821-1830

L.J. Jennings, M.E. Arcila, C. Corless, et al.Guidelines for Validation of Next-Generation Sequencing-Based Oncology Panels: A Joint Consensus Recommendation of the Association for Molecular Pathology and College of American PathologistsJ Mol Diagn, 19 (2017), pp. 341-365

M. Cristofanilli, G.T. Budd, M.J. Ellis, et al.Circulating tumor cells, disease progression, and survival in metastatic breast cancer

M. Garassino, D. Rodriguez-Abreu, S. Gadgeel, et al.OA04.06 Evaluation of TMB in KEYNOTE-189: Pembrolizumab Plus Chemotherapy vs Placebo Plus Chemotherapy for Nonsquamous NSCLC J Thoracic Oncol, 14 (2019), pp. S216-S217

M. Schwaederle, M. Zhao, J.J. Lee, et al. Association of Biomarker-Based Treatment Strategies With Response Rates and Progression-Free Survival in Refractory Malignant Neoplasms: A Meta-analysis JAMA Oncol, 2 (2016), pp. 1452-1459

M. Schwaederle, M. Zhao, J.J. Lee, et al.Association of Biomarker-Based Treatment Strategies With Response Rates and Progression-Free Survival in Refractory Malignant Neoplasms: A Meta-analysis JAMA Oncol, 2 (2016), pp. 1452-1459

M.M. Li, M. Datto, E.J. Duncavage, et al.Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American PathologistsJ Mol Diagn, 19 (2017), pp. 4-23

N Engl J Med, 351 (2004), pp. 781-791

P. Comoli, P. Pedrazzoli, R. Maccario, et al. Cell therapy of stage IV nasopharyngeal carcinoma with autologous Epstein-Barr virus-targeted cytotoxic T lymphocytes J Clin Oncol: Off J Am Soc Clin Oncol, 23 (2005), pp. 8942-8949

S. Cooley, F. He, V. Bachanova, et al First-in-human trial of rhIL-15 and haploidentical natural killer cell therapy for advanced acute myeloid leukemia Blood Adv, 3 (2019), pp. 1970-1980

S. Pabla, J.M. Conroy, M.K. Nesline, et al.Proliferative potential and resistance to immune checkpoint blockade in lung cancer patients J Immunother Cancer, 7 (2019), p. 27

S.A. Rosenberg, J.C. Yang, R.M. Sherry, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy Clin Cancer Res: Off J Am Assoc Cancer Res, 17 (2011), pp. 4550-4557

Scott, A. M., Allison, J. P., and Wolchok, J. D. (2012). Monoclonal antibodies in cancer therapy. Cancer Immun. 12:14

T.J. Hiltermann, M.M. Pore, A. van den Berg, et al.Circulating tumor cells in small-cell lung cancer: a predictive and prognostic factor Ann Oncol, 23 (2012), pp. 2937-2942

T.N.M. Schumacher T-cell-receptor gene therapy Nat Rev Immunol, 2 (2002), pp. 512-519

U. Sahin, E. Derhovanessian, M. Miller, et al Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer Nature, 547 (2017), pp. 222-226

Vile, R. G., Russell, S. J., and Lemoine, N. R. (2000). Cancer gene therapy: hard lessons and new courses. Gene Ther. 7, 2–8