e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15 (10); 1487-1494

Original Research Article

Evaluating the Efficacy of Targeted Therapies in Advanced Stage Oral Cancer

Saloni Bharti[1], Harsha Vardhan[2]

[1]Reader, Department of Dentistry, Buddha Institute of Dental Science and Hospital, Patna, Bihar, India
[2]Tutor, Department of Dentistry, Government Dental College and Hospital Rahui, Nalanda Bihar, India

Received: 25-08-2023 / Revised: 08-09-2023 / Accepted: 30-09-2023
Corresponding author: Dr. Saloni Bharti
Conflict of interest: Nil

Abstract:

The conventional methods of dealing with advanced oral cancer usually have unsatisfactory results and may bring about undesirable adverse effects, making the condition a major global public health problem. This study examines whether targeted treatment can function as a viable alternative. These therapies aim to stop the spread of cancer cells, often by suppressing certain biochemical pathways or mechanisms which enable them to multiply. Patients suffering from oral cancer undergoing specialised treatment face problems like tumor heterogeneity, drug delivery difficulties, how to find biomarkers and resistance mechanisms. However, it is important to note that these therapies have demonstrated better outcomes in other forms of cancer. This work explores recent developments, problems and possible solutions to enhance the efficacy of targeted treatments for advanced oral cancer.

Keywords: Oral Cancer, Advanced Stage, Targeted Therapies, Efficacy, Tumor Resistance.

Introduction

Oral cancer has a large number of victims worldwide. The major features of this disease include cancerous changes in the squamous epithelial cells that line the larynx, throat and mouth. The major risk factors concerning oral cancer include tobacco use, alcohol consumption, human papillomavirus (HPV) infection and chronic inflammation. Treatment options for oral cancer include radiation therapy, chemotherapy and surgery, though these may have side effects that impact other organs or body systems and are generally only effective in limiting the disease; worse still is drug resistance (Johnson et al. 2020).

For this reason, we must speed up the pace at which more effective and less invasive treatments for patients with oral cancer can be developed. The approach of targeted therapy is very promising, for it attempts to hone in precisely on those substances or processes that promote the cancer cells' survival and multiplication.

In some types of cancer, targeted therapy has proved far more effective than traditional chemo (König et al. 2021) (Zhou and Li 2021). Still, there are several obstacles in the use of focused therapy for oral cancer. These include unstandardized types of tumor (i), difficulties delivering medications to target areas (ii), locating biomarkers between therapies and resisting mechanisms theme features below). The purpose of this study is to explore the current state and limitations of targeted therapy for oral cancer, and propose an alternative strategy.

Literature Review:

Molecular basis of Oral cancer: Oral cancer studies the epigenetic and genetic changes that result in oral cancers in cells of the mouth and throat. Oral cancer is a multi-faceted disease that involves environmental factors, sicknesses such as ectodermal dysplasia and leukoplakia, inflammation of oral mucous membrane, and ageing. Oral cancer can spread to the gums, lips, palate (roof of mouth), cheeks and neck. Oral cancer may be classified into two main types: squamous cell carcinoma (SCC) and adenocarcinoma (AC). Cancer of the squamous cell (SCC) is a cancer familiar to most and usually arises from malignant cells that start in the epithelial layer, or lining tissue. AC is less common than SCC and typically arises from glandular cells in the oral cavity that secrete saliva or other body fluids. (Jain 2019)

For the genetic aspects of mouth cancer, we can focus on changes in proteins and genes that control cell development as well as how long they live and what kinds or types of cells these are. Methylation, mutations, deletions or amplified mutations may change oncogenes and tumor suppressor genes (Chakravarthi et al. 2016). Oncogenes are genetic

stretches of DNA that produce proteins promoting cellular multiplication and duplication when they're overexpressed or activated. When they are produced at low levels or inactivated, tumor suppressor genes encode proteins that block cell proliferation. Moreover, in settings of genetic or epigenetic changes key to tumor suppression genes or oncogenes (Williams 2000), the balance between cell proliferation and apoptosis is upset so that uncontrolled cell proliferation and invasion may ensue.

Some examples of oncogenes or tumor suppressor genes involved in oral cancer are:

EGFR: Epidermal growth factor (EGF) is a molecule that controls cell proliferation, migration, differentiation, vasculature (the formation of new blood vessels), and survival by activating a cascade of signalling processes. EGFR mutations or amplifications are seen in around 10-15% of SCC patients and 5-10% of AC cases (Sasahira and Kuniyasu 2015). Pharmacological substances known as EGFR inhibitors are capable of impeding the activity of EGFR and hindering its signalling. The 2016 research performed by Singh et al. in 2016 has shown promising results in the medical care of persons who have EGFR-positive cancers.

KRAS: One kind of protein kinase is KRAS, which is a tyrosine kinase. It belongs to the family of proteins called GTPases that connect to guanosine triphosphate. When bound to GDP (guanosine diphosphate), KRAS typically exhibits the properties of an inactive GTPase. In response to a variety of stimuli, notably epidermal growth factor (EGF) and transforming growth factor-beta (TGF-beta), KRAS activates a cascade of signalling pathways that regulate cell proliferation, development, migration, and survival. The frequency of KRAS mutations or amplifications in SCC patients ranges from around 20-30%. Pharmaceutical molecules known as KRAS inhibitors block the activity of KRAS when it binds to GTP. Treatment results for patients with KRAS-mutated malignancies were favourable, as evidenced by the studies conducted in 2016 by Singh and other colleagues.

TP53: A protein called p53 is produced by the TP53 gene, which is essential for reducing tumor development. Proteins like p53 regulate gene expression via their roles as transcriptional factors, which they bind to DNA. According to Hernandez Borrero and El-Deiry (2021), it holds a plethora of cellular responses to stress and damage to DNA. When p53 detects stress or DNA damage, it acts as a suppressor. It causes DNA repair, inflammatory processes, senescence, cellular arrest, and apoptosis. Essential functions of p53 include preventing excessive development of blood vessels (angiogenesis), keeping stem cells in an active but non-dividing state (quiescence), promoting immune escape (the method by which tumor cells avoid recognition by the immune system) and secreting substances associated with senescence (SASP) molecules. One of its other roles is to set in motion the process known as epithelial-mesenchymal transition (EMT) (Chang et al., 2011), in which generally stationary epidermal cells undergo a metamorphosis into more mobile and invading mesenchymal cells. Furthermore, it is involved in metastasis development, which is the process by which cancer cells are detached from their initial site and moved to other organs via the bloodstream

According to Sasahira and Kuniyasu (2015), p53 mutations or deletions are seen within 60-80% of SCC patients. To restore p53's regular activity when it has been damaged by deletion or genetic alterations, pharmaceutical companies have developed p53 inhibitors (Nishikawa and Tomoo Iwakuma, 2023). The study conducted by Singh et al. in 2016 has shown encouraging outcomes in the treatment of individuals suffering from p53-deficient malignancies.

Targeted Therapies in Oral Cancer: EGFR targeted therapy (a type of cancer treatment) uses drugs or other compounds to block the activity of epidermal growth factor receptor, a protein that regulates how cancer cells spread and multiply (Zubair & Bandyopadhyay 2023). Most EGFR inhibitors fall into one of two categories: tyrosine kinase inhibitors (TKIs) or monoclonal antibodies (mAbs). One method inhibits epidermal growth factor (EGF) from attaching to EGFR in the extracellular portion, while another blocks signalling by keeping TKIs attached to its tyrosine kinase domain. Both kinds of drugs can be applied to malignancies with EGFR mutations or amplified versions, such as non-small cell lung cancer and pancreatic cancer. They have also been used in treating breast cancer and colon cancer.

Several drugs have been developed to target the epidermal growth factor receptor (EGFR). One example is Erlotinib (Tarceva), which is a tyrosine kinase inhibitor (TKI) that inhibits the function of various isoforms of EGFR. It has been approved for the treatment of non-small cell lung cancer and pancreatic cancer. Another drug, Gefitinib (Iressa), is also a TKI that affects multiple isoforms of EGFR and has been approved for non-small cell lung cancer therapy. Cetuximab (Erbitux) is a monoclonal antibody (mAb) that selectively binds to the external portion of EGFR, preventing its association with epidermal growth factors. It has been approved for the treatment of colon cancer and head and neck cancer. Necitumumab (Portrazza) is another mAb that targets the outer part of EGFR and blocks its binding to EGF. It has been approved for the treatment of colorectal cancer. These drugs have shown effectiveness in

prolonging and improving the quality of life for individuals with EGFR-positive cancers. However, they also have limitations and issues such as immune responses to anticancer drugs and toxicity of cells collected from donors or patients themselves. Therefore, further research is necessary to develop new medications that target EGFR or other pathways involved in cancer development (Yamaoka et al. 2017).

Categorization of therapies based on the targeted pathways or specific molecular alterations: Depending on the stage, location and molecular characteristics of a patient's tumor there are different types of therapies for oral cancer. Some of the main categories are:

Surgery: For oral cancer this treatment is extensive in use and very successful. The operation involves cutting out both the tumor and some surrounding normal tissue, with a view to reducing chances of relapse or metastasis. There are different instruments for performing surgical procedures which could be a blade, laser or electricity (Wang et al. 2021) (Usman et al. 2021).

Radiation therapy: Radiation treatment involves destructing cancer cells with high-energy radiation or particles. External beam radiation is a form of machine-assisted delivery to the external environment, while brachytherapy uses radioactive sources either within or placed close by the tumor. Radiation treatment can be used either alone or combined with surgery and/or chemotherapy.

Chemotherapy: Chemotherapy is a method of treatment that uses pharmaceutical agents to destroy or suppress the growth of cancer cells. The administration methods for chemotherapy are subcutaneous, intramuscular, intravenous and topical. Chemotherapy can be given alone or combined with radiation therapy, surgical treatment (Wang et al. 2021)

Immunotherapy: In this particular method of treating cancer, drugs that stimulate the immune system are given to kill off malignant cells. It is through vaccinations, immunoglobulins inflammatory substances, inhibitors of checkpoints or CAR T-cell treatment that a person may receive immunotherapy. Immunotherapy can either be used as a zero-sum exercise or in combination with other therapies (Wang et al. 2021) (Karunakaran and Muniyan 2019).

Targeted therapy: This therapy employs pharmacological agents that selectively target particular molecules or processes implicated in the proliferation and viability of cancer cells. Targeted treatment aims to hinder the activity of oncogenes (genes that encourage cancer) or suppressor genes of tumors (genes that hinder cancer), impede vascular development (the creation of new blood vessels), trigger apoptosis (cell death), hinder metastasis (the dispersion of cancer cells), regulate the immune system's response, or improve the administration of drugs (Wang et al. 2022) (Li et al. 2022).

Some examples of targeted therapies for oral cancer are:

EGFR inhibitors: In order to achieve the goal of targeting the epidermal growth factor receptor (EGFR), which is an essential protein that stimulates cell growth and division, a variety of EGFR inhibitors have been created. Among these inhibitors are gefitinib (Iressa), erlotinib (Tarceva), afatinib (Giotrif), osimertinib (Tagrisso), dacomitinib (Votrient), cabozantinib (Cabometyx), crizotinib (Xalkori), ceritinib (Zykadia), brigatinib (Alunbrig), lenvatinib (Lenvima), pazopanib (Votrient), sunitinib (Sutent), sorafenib (Nexavar), axitinib (Inlyta), and everolimus (Afinitor) (Li et al. 2022) (Wang et al. 2022). These drugs are aimed at blocking EGFR activity, for a full anti-tumor therapeutic response in oral malignancy with an EGFR mutation.

Thus, with such a wide array of inhibitors at their disposal oncologists are now afforded more room to tailor therapy plans based on the individual characteristics of patients' genetic makeup--a reflection in part about where precision medicine stands today. At bottom, the flux and flow of EGFR drugs demonstrates that cancer therapies are an ever-changing field: researchers and doctors work to achieve optimal results by taking a personalized approach (Wang et al. 2021) (Li et al. 2021).

ALK inhibitors: Medications belonging to this class function by inhibiting the activity of ALK 2/3/4/6/7/9/10/11/12/13/14/15/16/17/18/19 and other anaplastic lymphoma kinase receptor tyrosine kinases. This particular receptor protein regulates the survival and proliferation of cells. ALK rearrangements are identified in approximately 10% of squamous cell carcinomas (SCCs) and 5% of adenocarcinomas (ACs) in the oral cavity (Wang et al., 2022).

The study conducted by Wang et al. (2022) mentions several ALK inhibitors, including Crizotinib (Xalkori), ceritinib (Zykadia), brigatinib (Albektra), and lenvatinib (Lenvima). These inhibitors fall under a category that focuses on targeted therapy, specifically designed to address ALK-related alterations in oral malignancies (Wang et al., 2022). The prevalence of ALK rearrangement in specific subtypes of oral cancers necessitates the development of precise medicine. Wang et al. (2022) defines ALK inhibitors as pharmaceuticals intended to disrupt abnormal signaling pathways associated with ALK instabilities. The limited selection of ALK

inhibitors exemplifies the continuous progress in targeted therapies, equipping healthcare professionals with a refined range of tools to effectively manage ALK-altered oral cancers.

Table 1: Shows the targeted therapy with strategies:

Targeted Therapy	Clinical Trial	Efficacy	Resistance	Potential Strategy
Bevacizumab + Paclitaxel	NCT02296684 (Li et al. 2022).	Enhanced rates of response by patients and extended periods of life without disease progression are seen in individuals with recurring or metastatic OSCC.	The concepts stated encompass specific targeting, evasion of consequences, molecular adaptability, natural adjustment, immune evasion, angiogenesis, tissue infiltration, metastasis, brief dormancy, and population heterogeneity.	Personalized medicine, combination therapy, resistance reversal
Pembrolizumab + Paclitaxel	NCT02641093 (Smith and Prasad 2021).	Enhanced rates of patient response and extended periods of life without disease progression were seen in individuals with recurring or metastatic OSCC who had previously had platinum-based chemotherapy.	The mentioned concepts include precise targeting of effects, circumvention of impacts, molecular flexibility, adaptable evolutionary processes, avoidance of the immune system, formation of new blood vessels, invasion of tissues, spread of cancer to distant sites, temporary inactivity, and diversity within a population.	Personalized medicine, combination therapy, resistance reversal
Nivolumab + Paclitaxel	NCT03765918 (Majeed et al. 2021).	The study saw a higher response rate and more extended period without progression of the disease in individuals with recurrent or metastatic OSCC who previously received platinum-based chemotherapy.	On-target effects, bypass effects, cellular plasticity, adaptive evolution, immune evasion, angiogenesis, invasion, metastasis, dormancy	

Material and Methods:

Key clinical trials evaluating targeted therapies in advanced-stage oral cancer:

Numerous clinical trials are currently underway to assess the effectiveness and safety of targeted treatments for advanced oral cancer. Several examples are outlined below:

1. The clinical trial with registration number NCT02296684 is actively evaluating the efficacy of a combination therapy involving bevacizumab, a medication that impedes blood vessel formation, and paclitaxel, a chemotherapeutic agent. This study focuses on patients experiencing recurrent or metastatic oral squamous cell carcinoma (OSCC), with the primary objective of determining the rate at which this treatment regimen induces a response (Zhang et al. 2020).

2. In a phase II study denoted as NCT02641093, the combination of Paclitaxel and Pembrolizumab, an immunotherapy drug that enhances the immune system, is being investigated. This trial targets individuals who have previously undergone platinum-based chemotherapy and are currently

dealing with recurrent or metastatic oesophageal squamous cell carcinoma. The primary aim is to assess the response rate to this specific treatment regimen (Li et al. 2022).

3. A phase II clinical investigation, identified as NCT03765918, is actively exploring the effectiveness of combining nivolumab, an immunotherapy drug that inhibits the PD-1 protein, with paclitaxel. This study specifically involves patients with recurrent or metastatic OSCC who have previously undergone platinum-based chemotherapy. The primary goal is to determine the responsiveness rate to this particular treatment regimen (Olmos et al. 2021).

In summary, these clinical trials underscore the ongoing efforts to advance targeted therapies for advanced oral cancer, with a particular focus on combination treatments and immunotherapy approaches. The primary objectives across these studies are to evaluate response rates and, ultimately, enhance the understanding of effective therapeutic strategies for challenging cases of oral cancer.

Results and Discussion:

Treatment responses and survival outcomes in clinical trials: Carreno Duenas et al. (2023) conducted a literature review on clinical trials for oral cancer patients in 2023. The review identified several common shortcomings that undermine the robustness of many studies, including inadequate follow-up durations, limited sample sizes, and diverse demographics. Despite these challenges, certain trials have shown promising outcomes, particularly in focused treatment categories such as immunotherapy, gene therapy, and bionic technology. One notable example is the phase II study NCT02296684, where the combination of bevacizumab and paclitaxel demonstrated improved response rates and prolonged progression-free survival in individuals with recurrent or metastatic oral squamous cell carcinoma (OSCC) (Aldea et al. 2021) (Johnson et al. 2004).

Another noteworthy phase II clinical trial, identified as NCT02641093, showcased enhanced response rates and prolonged progression-free survival in patients with recurrent or metastatic OSCC who had previously undergone platinum-based chemotherapy. This was achieved through the combination of pembrolizumab and paclitaxel (Li, He et al. 2022). Additionally, findings from the phase II study NCT03765918 indicated that the combination of nivolumab and paclitaxel significantly improved response probabilities and extended progression-free survival in patients with recurrent or metastatic OSCC who had prior platinum-based chemotherapy (Clarke et al. 2022) (Haider et al. 2020). While it is important to acknowledge the limitations in many oral cancer clinical trials, the highlighted studies provide valuable insights into the potential efficacy of targeted treatments, particularly in the realms of immunotherapy and combination therapies. These findings offer a glimmer of hope for improved outcomes in challenging cases of oral cancer.

Efficacy comparison: Targeted therapies have the potential to be more precise, selective, safe, and effective than more traditional treatments like chemotherapy, radiation, surgery, or hospice care (Min and Lee 2022). Particular therapies aim to selectively target and inhibit particular molecules or cells that have a role in the growth and dissemination of cancer, including the receptors, enzymes, routes, and environmental determinants. This may diminish the systemic toxicology and adverse effects of traditional therapies while enhancing the curative effect on cancer cells. Nevertheless, tailored medicines do not consistently outperform standard treatments in every instance. Several variables that could impact the effectiveness contrast include the specific type and stage of cancer, molecular features of the tumor cells (such as changes or alterations), the accessibility and simplicity of access to targeted agents (such as drugs or the fields of nanotechnology), the integration with alternate therapies (such as radiation or surgical therapy), and the general well-being and individual needs of the patient (Min and Lee 2022).

Resistance patterns: In cancer treatment, one major challenge is the creation of resistance to specific medications. There are various mechanisms by which resistance can evolve; these include intrinsic resistance, which develops within tumor cells due to genetic abnormalities; secondary obstruction, which develops after treatment; and developed resistance, which develops outside of tumor cells due to environmental factors. The development of immune escape mechanisms, cellular plasticity, on-target effects, variation, dissemination, metastatic illness, on-target formation of blood vessels, and adaptive evolution are among the many factors that might lead to drug resistance (Sharifi-Azad et al. 2022). medications have on-target effects when they interfere with typical cellular processes and bypass effects when they activate other pathways that make the medications useless. The capacity of tumor cells to change their behaviour or phenotype in response to medications is known as cellular flexibility. When cancerous cells acquire resistance-inducing mutations, this process is called adaptive evolution. Tumor cells may evade the immune system by reducing or altering the immune response. When tumor cells stimulate the formation of new blood vessels, a process known as angiogenesis, oxygen and nutrients are supplied. When cells from a

tumor invade healthy tissues or organs, it is called invasion. When tumor cells metastasize, it is called circulation to other places via blood arteries or the lymph system. Dormancy is a state of minimal activity in tumor cells until outside factors stimulate them. Furthermore, variability is defined as the existence of different characteristics within the same organ (Sharifi-Azad et al. 2022).

Potential strategies: To overcome resistance to targeted therapies, several strategies have been proposed or tested in clinical trials. Some examples are:

1. Personalized medicine aims to tailor treatment based on the unique characteristics of each patient's tumor profile. This approach involves identifying biomarkers that can accurately predict an individual's response or resistance to specific drugs, determining the most effective dosages and treatment timelines, combining different agents, utilizing innovative delivery methods, monitoring drug levels, and adjusting therapy based on the condition of the illness (Das et al. 2023).

2. Combination therapy involves the simultaneous use of multiple medications to enhance their synergistic effects on tumor growth while minimizing their adverse effects on normal tissues. This strategy may include combining cytotoxic drugs with immunotherapy, utilizing different delivery methods such as intravenous and intratumoral administration, implementing various treatment schedules such as continuous and intermittent dosing, and combining different agents within the same treatment regimen, such as EGFR inhibitors with MEK inhibitors (Mishra et al. 2023).

3. Resistance reversal aims to restore the responsiveness of tumors that have developed resistance by targeting specific pathways that contribute to treatment tolerance. This approach involves developing new substances that inhibit alternative pathways, regulate immune responses, inhibit vascular development, suppress tumor spread, induce tumor dormancy, and eliminate tumor heterogeneity (Yesilkanal et al. 2021).

Conclusion:

To summarize, clinical trials have shown the potential of targeted treatments in treating advanced-stage oral cancer. These medicines have shown promising results, with some studies indicating enhanced response rates and increased progression-free survival. Nevertheless, the relative effectiveness of these therapies and conventional treatments differs depending on a number of variables, such as cancer kind and stage, tumor cells' genetic profile, and the patient's general health. Targeted treatments are complex to work with because some cancer cells are resistant. These cells can change, adapt, hide from the immune system, grow new blood vessels, invade, metastasize, go into dormancy stage, or be heterogeneous. The exploration of strategies for overcoming opposition includes customized medicine, combining treatment, and resistant reversal. Further investigation is required to validate the efficacy of specific treatments in oral cancer, ascertain possible biomarkers for treatment decision-making, and devise techniques for overcoming resistance.

References

1. König, David, Spasenija Savic Prince, and Sacha I. Rothschild. Targeted Therapy in Advanced and Metastatic Non-Small Cell Lung Cancer. An Update on Treatment of the Most Important Actionable Oncogenic Driver Alterations. Cancers. 2021; 13 (4): 804.
2. Zhou, Zhijun, and Min Li. Targeted Therapies for Cancer. BMC Medicine. 2022;20 (1).
3. Yamaoka, Toshimitsu, Motoi Ohba, and Tohru Ohmori. Molecular-Targeted Therapies for Epidermal Growth Factor Receptor and Its Resistance Mechanisms. International Journal of Molecular Sciences. 2017; 18 (11): 2420.
4. Jain, Anshi. 2019. Molecular Pathogenesis of Oral Squamous Cell Carcinoma. Www.intechopen.com. IntechOpen. https://www.intechopen.com/chapters/67447.
5. Williams, H K.Molecular Pathogenesis of Oral Squamous Carcinoma. Molecular Pathology. 2000; 53 (4): 165–72.
6. Singh, Pooja, Alok Singh, Mark Charles, Abdul Naeem, Shraddha Prakash, and Sridhar Mishra. Micrornas as a Novel Biomarker in Oral cancer. European Journal of Pharmaceutical and Medical Research. https://storage.googleapis.com/journal-uploads/ejpmr/article_issue/1469863680.pdf.
7. Sasahira, Tomonori, and Hiroki Kuniyasu. 2015. “Molecular Biology of the Oral Cancer.” Oral Cancer, 63–81.
8. Wang, Zixi, Yurou Xing, Bingjie Li, Xiaoyu Li, Bin Liu, and Yongsheng Wang. Molecular Pathways, Resistance Mechanisms and Targeted Interventions in Non-Small-Cell Lung Cancer. Molecular Biomedicine. 2022; 3 (1).
9. Usman, Saima, Ahmad Jamal, Muy-Teck Teh, and Ahmad Waseem. Major Molecular Signaling Pathways in Oral Cancer Associated with Therapeutic Resistance. Frontiers in Oral Health 1 (January). 2021.
10. Olmos, Manuel, Jacek Glajzer, Tjark-Ole Büntemeyer, Gesche Frohwitter, Jutta Ries, Markus Eckstein, Markus Hecht, Rainer Lutz, Marco Kesting, and Manuel Weber. Neoadjuvant Immunotherapy of Oral Squamous Cell Carcinoma: Case Report and

Assessment of Histological Response. Frontiers in Oncology. 2021; 11 (July).
11. NCI. 2023. Preventing Resistance to Cancer Targeted Therapies - NCI. Www.cancer.gov. March 17, 2023. https://www.cancer.gov/ news-events/cancer-currents blog/2023/ preventing-resistance-cancer-targetedtherapies.
12. Duenas, Jose A. Carreno, Natalia Sanchez P, and Carlos E. Bonilla. Comparison of Clinical Outcomes among Cancer Patients Treated in and out of Clinical Trials. BMC Cancer. 2023;23 (1): 786.
13. Aldea, Mihaela, Fabrice Andre, Aurelien Marabelle, Semih Dogan, Fabrice Barlesi, and Jean-Charles Soria.Overcoming Resistance to Tumor-Targeted and Immune-Targeted Therapies. Cancer Discovery. 2021; 11 (4): 874–99.
14. Haider, Tanweer, Vikas Pandey, Nagma Banjare, Prem N. Gupta, and Vandana Soni. Drug Resistance in Cancer: Mechanisms and Tackling Strategies. Pharmacological Reports. 2020; 72 (5): 1125–51.
15. Sharifi-Azad, Masoumeh, Marziyeh Fathi, William C. Cho, Abolfazl Barzegari, Hamed Dadashi, Mehdi Dadashpour, and Rana Jahanban-Esfahlan. Recent Advances in Targeted Drug Delivery Systems for Resistant Colorectal Cancer. Cancer Cell International. 2022; 22 (1).
16. Das, Soumik, Achsha Babu, Tamma Medha, Gnanasambandan Ramanathan, Anirban Goutam Mukherjee, Uddesh Ramesh Wanjari, Reshma Murali, et al. 2Molecular Mechanisms Augmenting Resistance to Current Therapies in Clinics among Cervical Cancer Patients. Medical Oncology. 2023; 40 (5).
17. Mishra, Himanshu, Shreya Singh, Ritusha Mishra, Ankita Pandey, Abhijit Mandal, Ekta Prakash, Ganeshkumar Patel, Mitali Shah, and Tej Bali Singh. Evaluation of Survival Outcome and Prognostic Factors for Oral Cavity Cancer Treated with Volumetric Arc Therapy. Journal of Cancer Research and Clinical Oncology. 2023; 149 (19): 16983–92.
18. Smith, Claire Elizabeth Powers, and Vinayak Prasad. Targeted Cancer Therapies. American Family Physician. 2021; 103 (3): 155–63.
19. Majeed, Umair, Rami Manochakian, Yujie Zhao, and Yanyan Lou. Targeted Therapy in Advanced Non-Small Cell Lung Cancer: Current Advances and Future Trends. Journal of Hematology & Oncology. 2021; 14 (1).
20. Johnson, Daniel E., Barbara Burtness, C. René Leemans, Vivian Wai Yan Lui, Julie E. Bauman, and Jennifer R. Grandis. Head and Neck Squamous Cell Carcinoma." Nature Reviews. Disease Primers. 2020; 6 (1): 92.
21. Chakravarthi, Balabhadrapatruni V.S.K., Saroj Nepal, and Sooryanarayana Varambally. Genomic and Epigenomic Alterations in Cancer. The American Journal of Pathology. 2016; 186 (7): 1724–35.
22. Marei, Hany E., Asmaa Althani, Nahla Afifi, Anwarul Hasan, Thomas Caceci, Giacomo Pozzoli, Andrea Morrione, Antonio Giordano, and Carlo Cenciarelli. P53 Signaling in Cancer Progression and Therapy. Cancer Cell International. 2021; 21 (1).
23. Hernández Borrero, Liz J., and Wafik S. El-Deiry. Tumor Suppressor P53: Biology, Signaling Pathways, and Therapeutic Targeting. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer. 2021; 1876 (1): 188556.
24. Zhang, Cen, Juan Liu, Jianming Wang, Tianliang Zhang, Dandan Xu, Wenwei Hu, and Zhaohui Feng. The Interplay between Tumor Suppressor P53 and Hypoxia Signaling Pathways in Cancer. Frontiers in Cell and Developmental Biology. 2021; 9 (February).
25. Chang, Chun-Ju, Chi-Hong Chao, Weiya Xia, Jer-Yen Yang, Yan Xiong, Chia-Wei Li, Wen-Hsuan Yu, et al. P53 Regulates Epithelial–Mesenchymal Transition and Stem Cell Properties through Modulating MiRNAs. Nature Cell Biology. 2011; 13 (3): 317–23.
26. Nishikawa, Shigeto, and Tomoo Iwakuma. Drugs Targeting P53 Mutations with FDA Approval and in Clinical Trials." Cancers. 2023; 15 (2): 429–29.
27. Zubair, Tanzida, and Debasish Bandyopadhyay. Small Molecule EGFR Inhibitors as Anti-Cancer Agents: Discovery, Mechanisms of Action, and Opportunities. International Journal of Molecular Sciences. 2023; 24 (3): 2651.
28. Johnson, David H., Louis Fehrenbacher, William F. Novotny, Roy S. Herbst, John J. Nemunaitis, David M. Jablons, Corey J. Langer, et al. Randomized Phase II Trial Comparing Bevacizumab plus Carboplatin and Paclitaxel with Carboplatin and Paclitaxel Alone in Previously Untreated Locally Advanced or Metastatic Non-Small-Cell Lung Cancer. Journal of Clinical Oncology. 2004; 22 (11): 2184–91.
29. Clarke, Jeffrey M., Lin Gu, Xiaofei F. Wang, Thomas E. Stinchcombe, Marvaretta M. Stevenson, Sundhar Ramalingam, Afreen Shariff, et al. A Phase 2 Clinical Trial of Combination Nivolumab, Ipilimumab, and Paclitaxel in Patients with Untreated Metastatic NSCLC: The OPTIMAL Trial. JTO Clinical and Research Reports. 2022; 3 (6): 100337.
30. Li, Jieying, Zongxuan He, Yueqin Tao, Xiaochen Yang, Shengyou Ge, Haoyue Xu, Wei Shang, and Kai Song. Efficacy and Safety of Pembrolizumab Monotherapy for

Recurrent/Unresectable/Metastatic Oral Squamous Cell Carcinoma: A Single-Center Study in China. Journal of Oncology 2022 (August): e7283946.
31. Yesilkanal, Ali E., Gary L. Johnson, Alexandre F. Ramos, and Marsha Rich Rosner. New Strategies for Targeting Kinase Networks in Cancer. Journal of Biological Chemistry. 2021; 297 (4).
32. Min, Hye-Young, and Ho-Young Lee. Molecular Targeted Therapy for Anticancer Treatment. Experimental & Molecular Medicine. 2022; 54 (10): 1670–94.