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Review Article

Polypharmacology Strategies in Breast Cancer Treatment

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A B S T R A C T

Breast cancer is characterized by diverse molecular subtypes and intricate mechanisms of resistance, which pose formidable challenges to conventional single-target therapies. Polypharmacology represents a promising paradigm shift by simultaneously targeting multiple pathways and molecular targets implicated in tumor growth, metastasis, and treatment resistance. This multifaceted strategy not only enhances therapeutic efficacy but also addresses the dynamic interplay between cancer cells and their microenvironment. By integrating combinations of targeted therapies, immunomodulators, epigenetic modulators, and other agents, polypharmacology seeks to optimize treatment outcomes while mitigating the emergence of drug resistance—a pivotal obstacle in the long-term management of breast cancer.

Keywords: Polypharmacology, Breast cancer, drug resistance, Tumor growth

Introduction

Polypharmacology strategies in breast cancer treatment represent a pivotal shift in oncological therapeutics, aiming to overcome the complex and heterogeneous nature of this disease. Breast cancer, characterized by diverse molecular subtypes and mechanisms of resistance, poses significant challenges to traditional single-target therapies.[1] Polypharmacology offers a promising approach by concurrently targeting multiple pathways and molecular targets involved in tumor growth, metastasis, and treatment resistance. This multifaceted strategy not only enhances therapeutic efficacy but also addresses the dynamic interplay between cancer cells and their microenvironment. By leveraging combinations of targeted therapies, immunomodulators, epigenetic modulators, and other agents, polypharmacology seeks to maximize treatment outcomes while minimizing the development of drug resistance - a critical hurdle in long-term management of breast cancer.[2]

Current Landscape of Polypharmacology in Breast Cancer

Polypharmacology strategies in breast cancer treatment encompass a variety of approaches, including:

Multi-Targeted Small Molecules: Multi-targeted small molecules represent a promising approach in modern drug discovery and cancer therapy, aiming to address the complexity and adaptability of cancer cells by simultaneously targeting multiple key pathways and molecular targets crucial for tumor growth and survival. These molecules are designed with the capability to interact with several biological targets involved in various aspects of cancer biology, such as cell proliferation, angiogenesis, apoptosis resistance, and metastasis. By disrupting multiple pathways essential for tumor progression, multi-targeted small molecules offer several potential advantages over traditional single-target therapies.

One significant advantage is their ability to overcome inherent and acquired resistance mechanisms that often develop with single-target therapies. Cancer cells can evolve and adapt, rendering treatments ineffective over time. Multi-targeted small molecules, by hitting multiple targets simultaneously, can mitigate the development of resistance, thereby potentially extending treatment efficacy and improving patient outcomes.[3]

Moreover, these compounds may exhibit synergistic effects, where the combined action of targeting multiple pathways leads to greater therapeutic efficacy than the sum of individual effects. This synergism can enhance the effectiveness of treatment regimens, allowing for lower doses of individual drugs and potentially reducing adverse effects.

The development of multi-targeted small molecules involves a sophisticated understanding of cancer biology and molecular pathways. Advances in computational biology, structural biology, and medicinal chemistry play pivotal roles in identifying and designing these compounds. Computational tools enable the prediction of molecular interactions and the optimization of drug candidates with favorable pharmacokinetic and pharmacodynamic properties.

Clinical translation of multi-targeted small molecules involves rigorous preclinical testing to evaluate safety, efficacy, and pharmacological profiles. Early-phase clinical trials assess dose escalation, pharmacokinetics, and initial efficacy in patient populations, informing subsequent phases aimed at evaluating long-term safety and effectiveness.[4]

Combination Therapies: Combination therapies in the context of medicine, particularly in oncology, involve the strategic use of two or more treatments to enhance therapeutic efficacy, address multiple disease pathways, and mitigate treatment resistance. This approach contrasts with monotherapy, where a single treatment modality targets one aspect of the disease process. In cancer treatment, combination therapies are particularly critical due to the heterogeneous nature of tumors and the potential for cells to develop resistance to single agents over time.

The rationale behind combination therapies lies in the concept of synergy, where the combined effect of multiple treatments is greater than the sum of their individual effects. Synergy can occur through complementary mechanisms of action that target different pathways essential for tumor growth, such as inhibiting cell proliferation, inducing apoptosis, or blocking angiogenesis. By attacking cancer cells on multiple fronts simultaneously, combination therapies aim to achieve deeper and more sustained responses, reduce the likelihood of resistance development, and improve overall survival rates.[5]

There are several types of combination therapies used in clinical practice:

1. **Chemotherapy Combinations:** Combining different cytotoxic agents with non-overlapping toxicity profiles to enhance tumor cell kill while minimizing side effects on normal tissues.
2. **Targeted Therapy Combinations:** Pairing targeted agents that inhibit specific molecular targets or pathways implicated in cancer growth, such as combining a tyrosine kinase inhibitor with an anti-angiogenic agent in cancers driven by angiogenesis pathways.
3. **Immunotherapy Combinations:** Utilizing immune checkpoint inhibitors in combination with other immunomodulators or traditional therapies to enhance anti-tumor immune responses and overcome immune evasion mechanisms.
4. **Radiation Therapy Combinations:** Integrating radiation therapy with chemotherapy or targeted agents to potentiate local tumor control and address systemic disease.
5. **Precision Medicine Combinations:** Tailoring therapies based on individual tumor molecular profiles, biomarkers, and genetic mutations to optimize treatment response and minimize adverse effects.[6]

The development and optimization of combination therapies require rigorous preclinical evaluation to assess pharmacokinetics, pharmacodynamics, and potential interactions between agents. Clinical trials play a crucial role in determining safety, efficacy, and optimal dosing schedules in patient populations.

Immunomodulation: Immunomodulation refers to the therapeutic manipulation of the immune system to enhance or suppress its activity, aiming to achieve beneficial clinical outcomes in various disease contexts, including cancer, autoimmune disorders, and infectious diseases. In the realm of oncology, immunomodulation has emerged as a transformative approach to harnessing the body's immune defenses against cancer cells, leveraging the immune system's inherent ability to identify and eliminate abnormal cells.[7]

The immune system plays a crucial role in recognizing and eliminating cancer cells through a complex network of immune cells, cytokines, and signaling molecules. However, tumors can evade immune detection or create an immunosuppressive microenvironment, allowing them to proliferate unchecked. Immunomodulatory therapies seek to overcome these evasion mechanisms and bolster anti-tumor immune responses.

There are several key strategies of immunomodulation in cancer treatment:

1. **Immune Checkpoint Inhibitors:** These agents block inhibitory checkpoint proteins (e.g., PD-1, PD-L1, CTLA-4) on immune cells or tumor cells, thereby releasing the brakes on immune responses and enhancing T-cell-mediated cytotoxicity against cancer cells.

2. **Cytokine Therapy:** Administration of cytokines, such as interleukins (e.g., IL-2) and interferons (e.g., IFN-alpha), to stimulate immune cells and enhance their anti-tumor activity.
3. **Adoptive Cell Therapy:** Infusion of ex vivo expanded or genetically modified immune cells (e.g., CAR-T cells) into patients to target and destroy cancer cells with high specificity and potency.
4. **Vaccines and Immunotherapy Combinations:** Development of cancer vaccines or therapeutic vaccines that train the immune system to recognize tumor-specific antigens, combined with other immunomodulatory agents to enhance immune responses.
5. **Immunomodulatory Drugs:** Small molecule inhibitors or agonists targeting immune pathways to modulate immune cell functions and overcome immunosuppression within the tumor microenvironment.[8]

The success of immunomodulation in cancer treatment has revolutionized oncology, leading to durable responses and improved survival rates in a subset of patients across various cancer types. However, challenges remain, including identifying predictive biomarkers of response, managing immune-related adverse events, and overcoming resistance mechanisms.

Epigenetic Modulators: Epigenetic modulators are a class of compounds that regulate gene expression by modifying the structure and function of chromatin, without altering the underlying DNA sequence. These modulators play a critical role in determining which genes are activated or silenced within cells, influencing various biological processes, including development, differentiation, and disease states such as cancer.[9]

In cancer therapy, epigenetic dysregulation is a hallmark feature, where aberrant epigenetic modifications contribute to oncogenesis, tumor progression, and resistance to conventional therapies. Epigenetic modulators offer a novel therapeutic approach by targeting enzymes and proteins involved in chromatin remodeling, DNA methylation, histone modifications, and non-coding RNA regulation. By restoring normal epigenetic patterns or selectively altering gene expression profiles, these compounds aim to reverse oncogenic changes and restore cellular homeostasis.

There are several classes of epigenetic modulators currently under investigation:

1. **DNA Methyltransferase Inhibitors (DNMTis):** These agents block enzymes that add methyl groups to DNA, thereby reversing hypermethylation of tumor suppressor genes and promoting their re-expression in cancer cells.
2. **Histone Deacetylase Inhibitors (HDACis):** HDAC inhibitors target enzymes that remove acetyl groups from histone proteins, leading to chromatin relaxation and enhanced transcriptional activity of silenced genes involved in cell cycle regulation and apoptosis.
3. **Histone Methyltransferase Inhibitors (HMTis) and Demethylases (HDMis):** These inhibitors modulate enzymes responsible for adding or removing methyl groups from histone proteins, influencing chromatin structure and gene expression in cancer cells.
4. **Bromodomain and Extra-Terminal (BET) Inhibitors:** BET inhibitors target proteins that recognize acetylated histones, affecting transcriptional regulation of oncogenes and genes involved in cell survival pathways.
5. **Non-coding RNA Modulators:** Small molecules or oligonucleotides that target microRNAs or long non-coding RNAs involved in epigenetic regulation, altering gene expression patterns in cancer cells.[10]

Clinical studies have shown promising results with epigenetic modulators in various cancers, demonstrating their potential to enhance sensitivity to chemotherapy, radiotherapy, and immunotherapy. Challenges in the field include identifying biomarkers predictive of response, optimizing dosing regimens to minimize toxicity, and understanding the long-term effects on normal cellular function.

Natural Products and Traditional Medicines: Natural products and traditional medicines encompass a diverse array of compounds derived from plants, animals, fungi, and microorganisms, as well as formulations rooted in centuries-old medical practices. These substances have long been recognized for their therapeutic potential and are increasingly studied for their pharmacological activities and potential applications in modern medicine, including cancer treatment.

In oncology, natural products and traditional medicines offer a unique repertoire of bioactive compounds that can target various hallmarks of cancer, such as cell proliferation, apoptosis, angiogenesis, and metastasis.[11] Examples include:

1. **Plant-Derived Compounds:** Phytochemicals such as flavonoids (e.g., quercetin, epigallocatechin gallate), alkaloids (e.g., vincristine, paclitaxel), and polyphenols (e.g., resveratrol) have demonstrated anti-cancer properties by inhibiting tumor cell growth and inducing apoptosis.
2. **Marine Natural Products:** Compounds sourced from marine organisms, including sponges, algae, and corals, have yielded novel anticancer agents such as cytarabine (from sponges) and halichondrin B (from sea sponges), which exhibit potent cytotoxic effects against cancer cells.
3. **Traditional Chinese Medicine (TCM) and Ayurveda:** Herbal formulations and botanical extracts used in

TCM and Ayurvedic medicine, such as curcumin (from turmeric), ginsenosides (from ginseng), and triphala (a mixture of three fruits), have shown promising anti-cancer activities through mechanisms involving antioxidant effects, immune modulation, and inhibition of oncogenic pathways.

4. **Microbial Products:** Antibiotics, peptides, and secondary metabolites produced by microorganisms (e.g., actinomycetes) have been explored for their potential anticancer properties, such as bleomycin and doxorubicin.

Research into natural products and traditional medicines involves elucidating their mechanisms of action, pharmacokinetics, and safety profiles, as well as optimizing formulations for clinical use. Challenges include standardizing extracts, identifying active ingredients, and navigating regulatory pathways for approval.

Table 1. Approaches for Polypharmacology in Breast Cancer[11]

Approach	Description
Combination Therapies	Simultaneous use of multiple drugs targeting different pathways or molecular targets involved in breast cancer progression, such as HER2, PI3K/AKT/mTOR, and hormone receptors (ER/PR).
Sequential Therapies	Administration of drugs in sequence to exploit different stages of cancer cell growth and resistance mechanisms, optimizing treatment effectiveness over time.
Immuno-modulatory Agents	Incorporation of immune checkpoint inhibitors (e.g., PD-1/PD-L1 inhibitors) and other immunotherapies to enhance the body's immune response against breast cancer cells.
Epigenetic Modulators	Use of agents targeting epigenetic modifications (e.g., HDAC inhibitors, DNMT inhibitors) to alter gene expression patterns and restore normal cellular function in breast cancer.
Targeted Drug Delivery Systems	Utilization of nanoparticles, liposomes, or other advanced delivery systems to enhance drug specificity, improve bioavailability, and reduce systemic toxicity in breast cancer treatment.
Adaptive Therapy Approaches	Tailoring treatment regimens based on real-time patient data, biomarker analysis, and treatment response monitoring to optimize therapeutic outcomes and minimize resistance development.
Personalized Medicine Strategies	Integration of genomic profiling, biomarker analysis, and patient-specific characteristics to customize treatment plans and select the most effective polypharmacological approaches for individual patients.
Clinical Trials and Validation	Conducting rigorous clinical trials to validate safety, efficacy, and long-term benefits of polypharmacological approaches in diverse patient populations with breast cancer.

Benefits of Polypharmacology

The main advantages of polypharmacology in breast cancer treatment include:

Enhanced Therapeutic Efficacy: Enhanced therapeutic efficacy in medical treatment signifies the ability of therapies to achieve superior outcomes in managing diseases or conditions compared to standard approaches. This concept is particularly significant in fields like oncology, infectious diseases, and chronic conditions where treatment success profoundly impacts patient health and quality of life. Strategies that contribute to enhanced therapeutic efficacy include the development of therapies that target multiple disease pathways simultaneously, thereby achieving synergistic effects that improve overall response rates and disease control.[12] Overcoming resistance mechanisms, commonly seen in cancers and infectious diseases, is another crucial aspect. Therapies that employ polypharmacological approaches or combine agents with complementary mechanisms of action can mitigate resistance development, prolonging treatment effectiveness and delaying disease progression. Moreover, advancements in personalized medicine enable treatments to be tailored to individual patient profiles, optimizing therapeutic outcomes by selecting therapies most likely to benefit based on genetic, molecular, and clinical characteristics. Innovations in drug delivery systems further enhance efficacy by improving drug bioavailability and targeting specific tissues or cells while minimizing systemic side effects. Ultimately, achieving enhanced therapeutic efficacy not only improves treatment outcomes but also enhances patient safety, quality of life, and the overall management of complex medical conditions.

Reduced Resistance Development: Reduced resistance development in medical treatments represents a pivotal objective aimed at maintaining the long-term effectiveness of therapies against diseases that often adapt and become resistant over time. This challenge is particularly pronounced in fields such as oncology, infectious diseases, and chronic conditions where disease agents, including cancer cells and pathogens, can evolve mechanisms to evade or counteract treatment effects. Strategies to mitigate resistance development include employing combination therapies that simultaneously target multiple pathways or biological processes essential for disease survival. By attacking the disease from different angles, combination therapies decrease the likelihood of the disease acquiring resistance to all targeted mechanisms simultaneously.[13] Additionally, personalized medicine approaches tailor treatments based on individual genetic profiles and disease characteristics, allowing for precision targeting of vulnerabilities within disease cells and reducing the chances of resistance emergence. Advanced drug delivery systems further enhance efficacy by ensuring drugs reach their targets with optimal concentration, minimizing exposure to healthy tissues and reducing selective pressure for resistance development. Regular monitoring of treatment response and disease progression enables early detection of resistance mechanisms, facilitating timely adjustments to treatment regimens. Ultimately, by integrating these multidimensional approaches, healthcare providers aim to extend the duration of treatment effectiveness, improve patient outcomes, and address the evolving challenges of managing complex diseases effectively over time.

Personalized Treatment Approaches: Personalized treatment approaches in medicine represent a paradigm shift towards tailoring healthcare interventions to the individual characteristics of each patient. This concept acknowledges that every person's genetic makeup, lifestyle, environmental factors, and disease profile are unique, influencing their response to treatments. In practice, personalized medicine utilizes advanced technologies such as genomics, proteomics, and metabolomics to analyze biomarkers and genetic variations that underpin disease susceptibility and progression.[14] By identifying specific genetic mutations, biomarkers, or molecular signatures associated with a particular disease, healthcare providers can customize treatment strategies to maximize efficacy and minimize adverse effects. For instance, in oncology, molecular profiling of tumors can guide the selection of targeted therapies that directly inhibit aberrant pathways driving tumor growth, while sparing healthy tissues. Similarly, in infectious diseases, understanding microbial genomics can help predict drug resistance patterns and optimize antibiotic treatments. Personalized treatment approaches also extend to lifestyle modifications and preventive care, where individuals receive tailored recommendations based on their health risks and genetic predispositions. This individualized approach not only enhances treatment outcomes but also empowers patients to actively participate in their healthcare decisions, fostering a collaborative patient-provider relationship. As technologies continue to advance and our understanding of disease biology deepens, personalized treatment approaches are poised to revolutionize healthcare delivery, offering promise for more effective, efficient, and patient-centered medical care.[15]

Challenges and Considerations

Polypharmacology strategies in breast cancer treatment, which involve targeting multiple biological pathways or mechanisms simultaneously, offer promising avenues for improving therapeutic outcomes. However, several challenges and considerations must be navigated to maximize their effectiveness and safety in clinical practice.

1. **Complexity of Biological Interactions:** Breast cancer is a heterogeneous disease with diverse molecular subtypes and genetic profiles. Implementing polypharmacological approaches requires a deep understanding of the complex interactions between different signaling pathways involved in tumor growth, metastasis, and resistance mechanisms. Developing therapies that can effectively target multiple pathways while minimizing off-target effects remains a significant challenge.[16]
2. **Drug Resistance and Adaptation:** Like many cancers, breast tumors can develop resistance to therapies over time. Polypharmacology aims to mitigate this challenge by addressing multiple resistance mechanisms simultaneously. However, predicting and overcoming adaptive responses of cancer cells to combination therapies is a complex task that requires ongoing research and clinical validation.
3. **Safety and Toxicity Profiles:** Combining multiple drugs or agents in polypharmacological regimens can increase the risk of adverse effects and toxicity. Balancing efficacy with safety is crucial, as some combinations may have synergistic toxicities that limit their clinical utility. Optimizing drug dosing, administration schedules, and patient monitoring protocols are essential to minimize these risks.
4. **Clinical Trial Design and Regulatory Approval:** Conducting clinical trials to evaluate polypharmacological treatments involves specific challenges. Designing studies that adequately assess the efficacy and safety of combination therapies, defining appropriate endpoints, and interpreting complex data are critical considerations. Regulatory approval processes must also adapt to accommodate the unique characteristics of polypharmacological treatments.

5. **Cost and Accessibility:** The development and implementation of polypharmacological treatments may be cost-prohibitive, limiting access for certain patient populations or healthcare systems. Access to comprehensive genomic profiling and biomarker testing, which are integral to personalized polypharmacology, can also pose financial barriers and logistical challenges.[17]
6. **Patient Selection and Personalized Medicine:** Tailoring polypharmacological treatments based on individual patient characteristics, such as genetic mutations or biomarker profiles, is central to personalized medicine. However, identifying predictive biomarkers and determining which patients will benefit most from specific combinations remains a complex task that requires robust clinical validation.
7. **Educational and Training Needs:** Healthcare providers require specialized training and education to effectively implement polypharmacological strategies in breast cancer treatment. Keeping abreast of evolving research, understanding molecular diagnostics, and interpreting genomic data are essential competencies for oncologists and multidisciplinary teams involved in personalized cancer care.

Addressing these challenges requires collaborative efforts among researchers, clinicians, pharmaceutical companies, regulatory agencies, and patient advocates. Advancing polypharmacology in breast cancer treatment demands innovative approaches to drug discovery, rigorous clinical validation, comprehensive patient care pathways, and equitable access to cutting-edge therapies. Despite these challenges, the potential of polypharmacology to transform breast cancer treatment paradigms underscores its importance in the ongoing pursuit of precision oncology.[18]

Conclusion

Polypharmacology represents a promising frontier in breast cancer treatment, offering the potential to enhance therapeutic outcomes through multi-targeted approaches. As research advances and clinical trials progress, integrating polypharmacology with existing therapies and personalized medicine strategies holds the promise of transforming the landscape of breast cancer treatment, improving patient survival rates, and reducing treatment-related toxicity. Continued research efforts and collaborative initiatives are essential to realizing the full potential of polypharmacology in combating breast cancer and addressing the evolving challenges of this complex disease.

References

1. Acharya R, Pattanayak SP. Small Molecules Polypharmacology for the Treatment of Breast Cancer: A Roadmap for the Future Chemotherapy. Indian Journal of Pharmaceutical Education & Research. 2020 Apr 1;54(2).
2. Wang Z, Yang B. Polypharmacology in Clinical Applications—Anticancer Polypharmacology. InPolypharmacology: Principles and Methodologies 2022 Aug 2 (pp. 73-132). Cham: Springer International Publishing.
3. Ryszkiewicz P, Malinowska B, Schlicker E. Polypharmacology: promises and new drugs in 2022. Pharmacological Reports. 2023 Aug;75(4):755-70.
4. Calip GS, Xing S, Jun DH, Lee WJ, Hoskins KF, Ko NY. Polypharmacy and adherence to adjuvant endocrine therapy for breast cancer. Journal of oncology practice. 2017 May;13(5):e451-62.
5. Tomaselli D, Lucidi A, Rotili D, Mai A. Epigenetic polypharmacology: A new frontier for epi-drug discovery. Medicinal research reviews. 2020 Jan;40(1):190-244.
6. Zhang W, Bai Y, Wang Y, Xiao W. Polypharmacology in drug discovery: a review from systems pharmacology perspective. Current pharmaceutical design. 2016 Jun 1;22(21):3171-81.
7. Anighoro A, Bajorath J, Rastelli G. Polypharmacology: challenges and opportunities in drug discovery: miniperspective. Journal of medicinal chemistry. 2014 Oct 9;57(19):7874-87.
8. Wang Z, Yang B. Strategies of polypharmacology. InPolypharmacology: Principles and Methodologies 2022 Aug 2 (pp. 43-72). Cham: Springer International Publishing.
9. Hersh LR, Beldowski K, Hajjar ER. Polypharmacy in the geriatric oncology population. Current Oncology Reports. 2017 Nov;19:1-7.
10. Nightingale G, Mohamed MR, Holmes HM, Sharma M, Ramsdale E, Lu-Yao G, Chapman A. Research priorities to address polypharmacy in older adults with cancer. Journal of geriatric oncology. 2021 Jul 1;12(6):964-70.
11. Maggiore RJ, Gross CP, Hurria A. Polypharmacy in older adults with cancer. The oncologist. 2010 May 1;15(5):507-22.
12. Nightingale G, Skonecki E, Boparai MK. The impact of polypharmacy on patient outcomes in older adults with cancer. The Cancer Journal. 2017 Jul 1;23(4):211-8.
13. Sokol KC, Knudsen JF, Li MM. Polypharmacy in older oncology patients and the need for an interdisciplinary approach to side-effect management 1. Journal of clinical pharmacy and therapeutics. 2007 Apr;32(2):169-75.
14. Lichtman SM. Polypharmacy: geriatric oncology evaluation should become mainstream. Journal of Clinical Oncology. 2015 May 1;33(13):1422-3.
15. Sharma M, Loh KP, Nightingale G, Mohile SG, Holmes HM. Polypharmacy and potentially inappropriate

medication use in geriatric oncology. Journal of geriatric oncology. 2016 Sep 1;7(5):346-53.
16. Whitman A, DeGregory K, Morris A, Mohile S, Ramsdale E. Pharmacist-led medication assessment and deprescribing intervention for older adults with cancer and polypharmacy: a pilot study. Supportive Care in Cancer. 2018 Dec;26:4105-13.
17. Maggiore RJ, Dale W, Gross CP, Feng T, Tew WP, Mohile SG, Owusu C, Klepin HD, Lichtman SM, Gajra A, Ramani R. Polypharmacy and potentially inappropriate medication use in older adults with cancer undergoing chemotherapy: Effect on chemotherapy-related toxicity and hospitalization during treatment. Journal of the American Geriatrics Society. 2014 Aug;62(8):1505-12.
18. Prithviraj GK, Koroukian S, Margevicius S, Berger NA, Bagai R, Owusu C. Patient characteristics associated with polypharmacy and inappropriate prescribing of medications among older adults with cancer. Journal of geriatric oncology. 2012 Jul 1;3(3):228-37.