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Current Status, Challenges, and Prospects of Combining Immune Checkpoint Inhibitors and Chemotherapy in Non-Small Cell Lung Cancer Treatment

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Abstract: In recent years, significant advancements have been made in the use of immune checkpoint inhibitors (ICIs) for treating non-small cell lung cancer (NSCLC). Nevertheless, their efficacy as monotherapy remains limited in certain patient populations, especially in patients with low levels of PD-L1 expression. The combination of ICIs with chemotherapy has gradually emerged as a novel strategy, aiming to leverage the immune-enhancing effects of chemotherapy to synergize with ICIs. This review provides a comprehensive analysis of the synergistic mechanisms, clinical trial outcomes, safety and toxicity issues, resistance challenges, and future directions of ICI-chemotherapy combination therapy for NSCLC. Clinical evidence suggests that this combination notably extends progression-free survival (PFS) and overall survival (OS), demonstrating promising efficacy, particularly in advanced squamous NSCLC patients with low PD-L1 levels. By inducing immune enhancement through chemotherapy and activating immune responses via ICIs, this combined approach effectively overcomes the limitations of single-agent therapies. Despite a range of challenges, this immunotherapy combination offers renewed hope for improving treatment outcomes in NSCLC patients.

Keywords: Immune checkpoint inhibitor, non-small cell lung cancer treatment, chemotherapy.

1. Introduction

Lung cancer (LC) is recognized as one of the leading cancer types worldwide, with its incidence and mortality rates ranking first among all populations globally [1]. Despite being the most diagnosed cancer, lung cancer treatment faces significant challenges due to limited therapeutic options and efficacy, particularly as most patients are diagnosed at advanced stages. Contributing factors include industrialization-induced environmental changes and the widespread use of tobacco, which have sustained the high incidence and mortality rates of LC. Among all types, NSCLC is the most common, accounting for approximately 85% of all cases. Based on the morphological and histological characteristics of tumor cells, NSCLC can be further classified into subtypes, with adenocarcinoma and squamous cell carcinoma being the most prevalent, primarily linked to pollution exposure, genetic predisposition, and smoking [1].

In traditional treatment approaches, cisplatin-based doublet chemotherapy combined with surgery has been commonly employed as a first-line neoadjuvant therapy. Extensive clinical practices have

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demonstrated that this strategy is more effective than surgery alone in treating advanced NSCLC [2]. However, the non-specific targeting nature of chemotherapy often results in severe side effects and limited durability of efficacy. Recent years have witnessed significant advancements with immune checkpoint inhibitors (ICIs), which represent a pivotal shift in NSCLC treatment. ICIs-based immunotherapy works by blocking tumor-induced immunosuppressive signals, activating T lymphocytes and antigen-presenting cells to restore antigen recognition and enhance immune responses. This mechanism offers the potential for a more durable antitumor effect with less direct physical damage. However, variations in tumor characteristics and immune status among patients limit its effectiveness in a significant subset. Overactivation of the immune system can also lead to immune-related adverse events, and prolonged use frequently results in resistance, diminishing therapeutic outcomes.

Driven by these promising prospects, numerous clinical studies investigating the combination of ICIs and chemotherapy have been initiated, yielding encouraging results. This includes benefits such as enhanced treatment durability, extended progression-free survival (PFS) and overall survival (OS), as well as higher objective response rates. However, research remains inadequate in certain special populations, such as those with autoimmune diseases or early-stage NSCLC patients. The effectiveness of combination therapy in patients with low PD-L1 expression also warrants further exploration. Additionally, challenges persist, including increased risk of adverse effects in specific treatment regimens.

This article aims to comprehensively analyze the characteristics and challenges of chemotherapy and ICIs, discuss their synergistic mechanisms and advantages as a first-line treatment option, and review recent key clinical trials to identify existing challenges and outline directions for future research.

2. Characteristics and limitations of traditional chemotherapy-based neoadjuvant therapy

2.1. Characteristics

Chemotherapy exerts its effects through the cytotoxic inhibition of DNA replication and protein synthesis in cells. This mechanism is particularly effective against rapidly dividing and protein-synthesizing cells, such as cancer cells. As a result, chemotherapy is commonly administered as a neoadjuvant therapy prior to surgery to significantly reduce tumor size, downgrade the tumor stage, and decrease tumor activity, thereby inhibiting further progression. This approach not only lowers the complexity of surgical procedures and improves surgical success rates but also enables previously inoperable patients to become eligible for surgery [2]. Additionally, chemotherapy can effectively eliminate microscopic metastatic lesions, reducing the risk of postoperative recurrence and metastasis.

2.2. Advantages and limitations

Clinical practice has demonstrated that adjuvant therapy integrating chemotherapy with surgery moderately enhances the five-year survival rate compared to surgery by itself. However, individual variability among patients and the current lack of reliable biomarkers to predict chemotherapy responses make it challenging to deliver precise and targeted treatments. This variability can result in significant differences in chemotherapy effectiveness, with some cases failing to reduce tumor size and, in fact, potentially exacerbating tumor progression. Such outcomes may increase the complexity of surgical procedures, cause patients to miss the optimal timing for surgery, or render them ineligible for surgery altogether. Additionally, chemotherapy is associated with notable side effects, such as hair loss, damage to liver and kidney functions, bone marrow suppression, and a weakened immune system. When the therapeutic effect diminishes, recurrent patients may experience exacerbated symptoms and a further decline in quality of life.

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3. Characteristics and limitations of ICIs therapy

3.1. Characteristics

Tumor immunotherapy involving ICIs fundamentally aims to reactivate the body's immune system, leveraging its inherent capacity to suppress and eliminate tumors. This approach reduces tumor size, eradicates microscopic metastatic lesions, and inhibits tumor recurrence. PD-1/PD-L1 and CTLA-4 inhibitors exert their effects by binding to specific targets and preventing interactions with immune cells, including T cells, B cells, NK cells, and macrophages. By preventing the generation of inhibitory signals, these inhibitors restore T cell activity, promote their proliferation and differentiation, and enable effective tumor cell recognition and destruction [3]. At the same time, activating B cells and NK cells increases the levels of immune-related proteins in the tumor microenvironment (TME), such as cytokines, specific antibodies, and perforins. This targeted activation of the immune system harnesses the body's natural defenses to more effectively combat tumor cells.

3.2. Safety concerns and limitations

The use of ICIs is also associated with safety concerns. Acting as immune enhancers, ICIs not only block the inhibitory signals from tumor cells to immune cells but also suppress the anti-immune response signals of normal cells. This can lead to excessive activation of the immune system, where active immune cells may attack normal functional cells even after the tumor cells have been largely eliminated. Such immune overactivation may result in autoimmune diseases, imposing a significant long-term burden on the body's organs and potentially causing inflammatory conditions such as hepatitis, colitis, nephritis, and arthritis [4].

However, the efficacy of ICIs as monotherapy is limited in patients with low PD-L1 expression. These patients typically exhibit insufficient immune responses, with low immune cell activity within the TME, making it difficult for ICIs to effectively initiate an immune response. Additionally, prolonged treatment often leads to immune evasion and resistance. This is primarily due to tumor cells modulating their microenvironment to suppress T cell activity. Contributing factors to this complexity include driver gene mutations, the presence of M2 macrophages, regulatory T cells, myeloid-derived suppressor cells, and other inhibitory factors within the TME.

4. Mechanisms and advantages of ICIs-chemotherapy combination therapy

4.1. Synergistic mechanisms

Chemotherapy has a long history in the treatment of NSCLC, primarily reducing tumor burden by targeting rapidly dividing cells. However, its impact on the immune system extends far beyond traditional understanding. Research indicates that chemotherapy can trigger immunogenic cell death (ICD), leading to the release of abundant tumor antigens and activation of dendritic cells (DCs), which in turn boosts the antitumor function of T cells [5]. Concurrently, ICIs block inhibitory signals to T cells and other immune cells, synergizing with chemotherapy to maintain high levels of immune activation. Moreover, chemotherapy markedly transforms the tumor microenvironment (TME) by lowering the levels of immunosuppressive cells, including myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), while also reducing the production of immunosuppressive factors. This collaboration between chemotherapy and ICIs promotes increased T cell infiltration into the TME, further enhancing antitumor efficacy.

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4.2. Advantages of combination therapy

These effects create a more favorable antitumor environment for ICIs. This synergistic mechanism enhances the efficacy of combining chemotherapy with ICIs. Some studies have demonstrated that the immune microenvironment changes induced by combination therapy show certain efficacy even in patients with low PD-L1 expression levels [6]. Furthermore, multiple studies have indicated that the combination of ICIs and chemotherapy can significantly improve PFS, OS, and ORR in patients [7].

5. Analysis of key clinical trials

5.1. KEYNOTE-021 study

The KEYNOTE-021 clinical study aimed to evaluate the effectiveness and security of pembrolizumab in conjunction with various agents for the treatment of advanced NSCLC, exploring potential improvements in therapeutic strategies. Specifically, the trial investigated: (1) the potency of pembrolizumab combined with carboplatin and pemetrexed as the initial treatment for advanced non-squamous NSCLC; (2) the efficacy of pembrolizumab combined with erlotinib or gefitinib as first-line treatment for advanced EGFR-mutant NSCLC; and (3) the efficacy of pembrolizumab united with ipilimumab as second-line or subsequent-line treatment for advanced NSCLC.

The study incorporated patients with advanced NSCLC, such as untreated stage IIIB or IV non-squamous NSCLC patients without EGFR and ALK gene mutations, along with adult NSCLC patients possessing sensitizing EGFR mutations. All enrolled patients had a life expectancy of ⩾3 months, and tumor biopsy samples were evaluated for PD-L1 expression.

The outcomes were as follows:

1) Pembrolizumab plus carboplatin and pemetrexed: For first-line treatment of advanced non-squamous NSCLC, the combination cohort achieved an ORR of 58%, compared to 33% in the chemotherapy-alone group. The median PFS in the combination group was 24.5 months, as opposed to 9.9 months in the chemotherapy - alone group, signifying a 46% decrease in the risk of disease progression or death. The median OS in the combination group was 34.5 months compared to 21.1 months in the chemotherapy-alone group, reducing the risk of death by 29%. Regarding adverse events, 41% of patients in the combination group endured grade 3-5 toxicities, compared to 27% in the chemotherapy-alone group.

2) Pembrolizumab plus erlotinib or gefitinib: In the subgroup of patients with advanced EGFR-mutant NSCLC, the pembrolizumab + erlotinib combination achieved an ORR of 41.7%, with all patients expressing PD-L1 ⩾50% showing a complete response. The median PFS was 19.5 months, and the median OS was not reached. For the pembrolizumab + gefitinib combination, the ORR was 14.3%, with a median PFS of 1.4 months and a median OS of 13 months.

3) Pembrolizumab plus ipilimumab: As the second-line or subsequent-line treatment, the pembrolizumab + ipilimumab combination resulted in a median PFS of 4.1 months and a median OS of 10.9 months. The incidence of grade 3-5 treatment-related adverse events was 29%, and 20% of patients combined treatment due to adverse events.

These findings underscore the potential benefits and limitations of combining pembrolizumab with various agents in the treatment of advanced NSCLC, highlighting the need for continued optimization of therapeutic strategies.

5.2. KEYNOTE-189 study

The KEYNOTE-189 study aimed to appraise the efficaciousness of pembrolizumab in conjunction with chemotherapy as opposed to chemotherapy alone in previously untreated patients with metastatic

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non-squamous NSCLC without EGFR or ALK gene mutations. The study used OS and PFS as primary endpoints to assess which treatment regimen provided greater benefits to patients. Participants included treatment-naïve stage IV non-squamous NSCLC patients with driver gene-negative tumors. They were randomly assigned in a 2:1 ratio into two groups: Group A received pembrolizumab + pemetrexed + carboplatin/cisplatin for four cycles, followed by pembrolizumab maintenance therapy for up to 31 cycles and pemetrexed until disease progression; Group B received placebo + pemetrexed + carboplatin/cisplatin for four cycles, followed by placebo maintenance therapy for up to 31 cycles and pemetrexed until disease progression.

The results of the study disclosed that, after a median follow-up period of 10.5 months, the median OS had not been attained in the pembrolizumab combination group, whereas it was 11.3 months in the chemotherapy-only group. The 12-month OS rates for the combination and chemotherapy groups were 69.2% and 49.4%, respectively. The median PFS was 8.8 months in the combinatorial group and 4.9 months in the chemotherapy-alone group, with 12-month PFS rates of 34.1% and 17.3%, respectively, representing a 48% diminution in the risk of death. The Objective Response Rate (ORR) was 47.6% in the combination group compared to 18.9% in the chemotherapy group, with a median duration of response of 11.2 months and 7.8 months, respectively. Notably, the combination group demonstrated higher response rates irrespective of PD-L1 expression levels.

This study strongly supports the synergistic effect of combining immunotherapy with chemotherapy in the treatment of NSCLC. Even patients with PD-L1-negative or low-expression tumors achieved significant survival benefits, challenging the previous notion that immunotherapy is only effective in patients with high PD-L1 expression. By expanding the applicability of immunotherapy, the significant survival enhancements witnessed in this study led to a paradigm shift in the first-line treatment guidelines for advanced NSCLC. The combination of pembrolizumab and chemotherapy has now emerged as a standard first-line treatment for such patients, providing clinicians with robust evidence and advancing the field of LC treatment.

5.3. KEYNOTE-047 study

The KEYNOTE-407 study aimed to assess the efficacy and safety of pembrolizumab in combination with carboplatin and paclitaxel as a first-line treatment for patients with metastatic squamous NSCLC lacking epidermal EGFR and anaplastic lymphoma kinase (ALK) gene mutations.

The study found that, after a median follow-up of 10.4 months, the median OS was 17.3 months in the pembrolizumab combination group compared to 12.6 months in the chemotherapy-only group. The median PFS was 8.3 months in the combination group versus 4.2 months in the chemotherapy group. These results indicate that the combination of ICIs and chemotherapy can significantly elevate survival. The ORR was 57.9% in the combination group, higher than the 38.4% observed in the chemotherapy-only group. Markedly, the combination therapy demonstrated superior median PFS and OS regardless of patients' PD-L1 tumor proportion score (TPS) status, suggesting that the combination therapy can enhance treatment efficacy across diverse patient subgroups. Importantly, the safety profiles of the two cohorts were similar, although the combination cohort showed higher rates of chemotherapy dose reductions and interruptions in any treatment component, reflecting a manageable safety profile.

This study has significant clinical implications. For patients with advanced squamous NSCLC, traditional chemotherapy has shown limited efficacy. The KEYNOTE-407 study demonstrated the remarkable therapeutic benefits of combining immunotherapy with chemotherapy in this patient population, overcoming previous limitations in the treatment of advanced squamous NSCLC. It further expanded the scope of immunotherapy in LC treatment, enabling more patients to benefit from this approach. Consequently, the KEYNOTE-407 study broadened the applicability of

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immunotherapy and supported updates to clinical treatment guidelines, establishing pembrolizumab combined with chemotherapy as a standard first-line treatment for this patient group.

5.4. CheckMate-227 study

The CheckMate-227 clinical research was directed towards assessing the effectiveness and security of nivolumab, nivolumab combined with ipilimumab, and nivolumab combined in comparison to platinum-based doublet chemotherapy versus platinum-based doublet chemotherapy as first-line treatments for advanced NSCLC.

The study enrolled patients with stage IV or recurrent NSCLC who had not received prior treatment. Participants were randomized into the following groups: (1) the nivolumab plus ipilimumab group, which received nivolumab and ipilimumab in combination; (2) the nivolumab plus chemotherapy group, which received nivolumab combined with platinum-based doublet chemotherapy; and (3) the chemotherapy-only group, which received platinum-based doublet chemotherapy alone.

The research outcomes indicated that within the group of 299 patients having a high tumor mutational burden (TMB) (≥10 mutations per megabase), the PFS in the nivolumab plus ipilimumab combination was considerably l longer than that in the chemotherapy group, with a hazard ratio (HR) of 0.58 (P = 0.0002). The 1-year PFS rates were 43% and 13%, respectively, and the 1-year duration of response rates were 68% and 25%, respectively. The ORR was also greater in the nivolumab plus ipilimumab combination in comparison to the chemotherapy group (45.3% vs. 26.9%). Among patients with high TMB and PD-L1-positive tumors, the nivolumab plus ipilimumab combination further enhanced PFS compared to nivolumab monotherapy, with a 1-year PFS rate of 42% versus 29%.

This study was the first to establish TMB as a predictive biomarker for immunotherapy, validating its importance in predicting the benefits of nivolumab combined with ipilimumab. The findings provide a new basis for precision medicine in patients with advanced NSCLC. The results demonstrated the efficacy and safety of nivolumab plus ipilimumab as a first-line treatment for patients with high TMB advanced NSCLC, offering a novel therapeutic option for this population and redefining the first-line treatment landscape for advanced NSCLC. More importantly, the CheckMate-227 findings have propelled further exploration and research into combination immunotherapy regimens for advanced NSCLC and other tumor types, offering valuable insights for developing more effective immunotherapy strategies.

6. Challenges and future directions

6.1. Limitations in efficacy and resistance challenges

6.1.1. Safety and toxicity

Although ICIs combined with chemotherapy have shown improved efficacy, challenges remain in managing toxicity. Chemotherapy is often associated with side effects such as fatigue, nausea, and anemia, while ICIs can induce immune-related adverse events (irAEs), including pneumonitis, colitis, and endocrine dysfunction. The safety concerns of combination therapy generally encompass those of both treatments. Studies have shown that chemotherapy combined with PD-L1/CTLA-4 inhibitors increases the risk of moderate to severe (grade 3-5) adverse events, with an overall higher incidence of side effects. However, with appropriate dose adjustments, close monitoring, and supportive care during treatment, the toxicity is generally within an acceptable range, indicating a relatively favorable safety profile [8].

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6.1.2. Monitoring and sustaining treatment efficacy

As most NSCLC patients are diagnosed at advanced stages, the effectiveness and safety of combination immunotherapy in early- to mid-stage cases remain uncertain. Real-time monitoring of patient conditions is required to guide combination therapy and refine related clinical data. Additionally, combination immunotherapy often relies on biomarkers such as PD-L1 and PD-1 to assess patient response and suitability. However, the expression levels of these biomarkers are influenced by multiple factors, and patient adaptability to treatment may also be regulated by specific gene expressions in the TME. The current reliability of biomarkers thus requires further improvement.

While combination immunotherapy enhances efficacy through the synergistic use of multiple agents, the increased demand for drugs and the complexity of the regimen impose significant financial burdens on healthcare institutions and patients' families. This makes implementation particularly challenging in regions with underdeveloped healthcare systems, posing higher demands on the optimization of dosing regimens.

6.1.3. Resistance challenges

Although chemotherapy induces immunogenic cell death and exposes hidden antigens, thereby reducing the impact of resistance when combined with ICIs, specific genetic mutations (e.g., EGFR, KRAS) can alter the composition of the TME. These alterations lead to reduced responsiveness to targeted and chemotherapeutic agents and may promote tumor progression and phenotypic transformation. Multiple factors contribute to the development of complex resistance to combination immunotherapy, which diminishes objective response rates and adversely affects PFS and OS [9].

Therefore, considering the current safety, efficacy, and susceptibility to resistance in NSCLC treated with chemotherapy combined with ICIs, several future research directions for combination immunotherapy in NSCLC can be proposed:

6.2. Future development directions

6.2.1. Ensuring the safety of combination therapy

Adjustment of Drug Dosage and Treatment Duration: Tailoring the dosage and duration of chemotherapeutic and immunotherapeutic agents based on individual patient characteristics, such as age, physical condition, and organ function, is essential. Efforts should focus on exploring lower-dose chemotherapy regimens that maintain efficacy while minimizing toxicity to normal tissues, without compromising the synergistic effects of immunotherapy. Conducting relevant clinical trials is crucial to establish optimal strategies for dose adjustment.

Improvement of Adverse Event Management Strategies: Developing a comprehensive system for monitoring and managing adverse events is necessary. New drugs or therapeutic approaches should be designed to mitigate specific adverse effects associated with combination therapy, such as irAEs and chemotherapy-induced bone marrow suppression, nausea, and vomiting. For severe irAEs like immune-related pneumonitis, research into more effective corticosteroid alternatives or immunomodulatory treatments is particularly needed [10].

6.2.2. Enhancing the effectiveness of combination therapy

Precision Selection of Treatment Populations: Identifying patient populations most likely to benefit from combination chemotherapy and immunotherapy, while also tolerating the treatment, requires more precise biomarkers. In addition to the commonly used PD-L1 expression levels, further research

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into other immune-related molecular markers, TMB, and gene expression signatures is essential to predict patient responses to combination therapy and the risk of adverse events.

Exploration of New Treatment Modalities: Investigating optimal sequencing and alternation strategies for chemotherapy and immunotherapy is critical. For instance, initiating chemotherapy to modulate the TME and release tumor antigens, followed by immunotherapy, could enhance immune activation. Alternatively, alternating therapies might prevent tumor cells from developing resistance under different drug pressures. Preclinical studies and clinical trials are needed to determine the best sequential or alternating regimens for different NSCLC subtypes, such as squamous cell carcinoma and adenocarcinoma.

Mechanisms: Comprehensive investigation into the resistance mechanisms of NSCLC during combination chemotherapy and immunotherapy is essential. This includes analyzing intrinsic tumor cell factors, such as alterations in signaling pathways and defects in antigen presentation, as well as TME factors, such as the accumulation of immunosuppressive cells and changes in cytokine profiles. These analyses provide a theoretical basis for developing targeted strategies to overcome resistance.

Development of Post-Resistance Treatment Strategies: Based on resistance mechanism studies, post-resistance treatment strategies should be developed. For patients with immune resistance, alternative ICIs or combinations with other immunomodulatory agents can be explored to reactivate antitumor immune responses. In cases of chemotherapy resistance, the introduction of new chemotherapeutic agents or the use of targeted therapies may be effective. Additionally, research should focus on how to readjust the combination of chemotherapy and immunotherapy after resistance occurs to restore treatment efficacy.

Early Resistance Monitoring and Intervention: Establishing effective methods for early resistance monitoring is critical. This can be achieved through liquid biopsies (e.g., detecting circulating tumor cells and ctDNA), imaging techniques (e.g., functional imaging modalities like PET-CT), and biomarker surveillance. Once signs of resistance are detected, treatment regimens should be promptly adjusted, such as increasing drug dosages, switching agents, or incorporating additional therapies. These interventions aim to delay the onset and progression of resistance, thereby improving long-term treatment outcomes.

7. Conclusion

Studies and analyses on the combination of ICIs and chemotherapy have yielded numerous positive outcomes, including the advantages of sustained treatment, significant improvements in PFS and OS, and enhanced ORR. The synergistic effects of these therapies establish them as a viable first-line treatment option for patients with advanced NSCLC.

Despite these benefits, the analysis highlights persistent challenges in managing resistance and toxicity, particularly in addressing moderate-to-severe adverse effects and maintaining long-term efficacy. Additionally, there is considerable variability in patient adaptation to combination therapy, emphasizing the need for further optimization of biomarker selection and efficacy prediction. Nevertheless, by summarizing findings from multiple studies and trials, this review underscores the mechanistic advantages of combination therapy, laying a solid foundation for developing future treatment strategies.

This review integrates a multi-perspective analysis and comprehensive data synthesis, emphasizing the pivotal role of combination therapy in improving patient survival while identifying current limitations. It provides clear directions for future research, including further exploration of resistance mechanisms, development of more precise biomarkers, and optimization of dosing strategies to achieve personalized treatment. These advancements will offer valuable guidance for the broader application of combination therapy in NSCLC and inject new momentum into the field of LC treatment.

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Overall, the combination of ICIs and chemotherapy represents a promising avenue for NSCLC treatment. However, realizing its full potential will require sustained research and continued clinical practice.

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