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Platinum Plus Immunotherapy Versus Platinum Alone in Triple-Negative Breast Cancer: A Systematic Review

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ABSTRACT

Triple-negative breast cancer (TNBC) represents approximately 15–20% of all breast cancers and is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression [1]. TNBC is associated with aggressive clinical behavior, higher rates of visceral metastasis, earlier recurrence, and poorer overall prognosis compared to other breast cancer subtypes [1],[19]. Cytotoxic chemotherapy has historically remained the mainstay of systemic treatment [1]. Among available agents, platinum compounds such as carboplatin and cisplatin have demonstrated particular activity because TNBC frequently exhibits defects in homologous recombination DNA repair pathways, including BRCA1/2 dysfunction[2],[4] In recent years, immune checkpoint inhibitors against programmed death-1 (PD-1) or programmed death-ligand 1(PD-L1) have emerged as promising therapeutic strategies [7],[8][15]. Combining immunotherapy with platinum-based chemotherapy may enhance antitumor immunity and improve outcomes [14], [15]. To conduct a systematic review of existing evidence that contrasts the use of platinum combined with immunotherapy against platinum alone in individuals with early-stage and metastatic TNBC, with an emphasis on evaluating efficacy, survival rates, pathological complete response, and safety.[4],[14] Significant trials such as KEYNOTE-355[7], KEYNOTE-522[9],[16], IMpassion130, IMpassion031, GeparNuevo, NeoTRIPaPDL1, along with various pooled analyses[4],[14],[20], have shown enhanced pathological complete response (pCR), progression-free survival (PFS), event-free survival (EFS), and overall survival (OS) in specific TNBC groups receiving platinum combined with immunotherapy, as opposed to chemotherapy alone. The advantages were particularly evident in PD-L1-positive metastatic TNBC and early-stage II–III TNBC [9],[10],[16]. Nonetheless, the incidence of immune-related adverse events was higher in the arms receiving combination therapy [7],[8],[9],[15]. Conclusion present data indicate that combining platinum with immunotherapy offers a more effective treatment approach than using platinum by itself for carefully chosen patients with TNBC [14], [15]. It remains crucial to select patients based on biomarkers and to manage toxicity effectively[13],[15].

Keywords: Triple-negative breast cancer, Platinum chemotherapy, Carboplatin, Cisplatin, Immunotherapy, Pembrolizumab, Atezolizumab, Durvalumab , PD-1 inhibitor , PD-L1 inhibitor, KEYNOTE-355 , KEYNOTE-522, IMpassion130

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INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy among women worldwide, and is one of the leading causes of cancer-related mortality [1], [3]. Triple-negative breast cancer (TNBC) is a biologically heterogeneous subtype accounting for approximately 15–20% of invasive breast cancers [1], [19]. It is characterized by the lack of ER and PR expression and absence of HER2 overexpression or gene amplification. Because endocrine therapy and HER2-directed therapies are ineffective, systemic chemotherapy has traditionally been the only therapeutic option [2],[3]. Aggressive clinicopathologic characteristics of TNBC include: high histological grade, a higher proliferative index, recurrence earlier, especially in the first three years, increased risk of brain and visceral metastases, and decreased survival following recurrence. Many patients exhibit treatment resistance and recurrence despite initial chemosensitivity[18],[19]. Therefore, novel therapeutic approaches are urgently needed. Double-strand breaks and DNA cross-linking are caused by platinum compounds such as carboplatin and cisplatin. In tumors with faulty homologous recombination repair pathways, particularly BRCA1/2-mutated malignancies, their effectiveness is increased. Platinum therapy is an attractive approach because a significant proportion of TNBC demonstrates "BRCAness" or genomic instability. Simultaneously, TNBC is considered one of the most immunogenic breast cancer subtypes because of [1],[13].[15]:

- Higher tumor-infiltrating lymphocytes (TILs)
- Greater PD-L1 expression
- Increased neoantigen burden
- Higher genomic instability
- Enhanced immune microenvironment activation

The results offer compelling support for combining immune checkpoint inhibitors with chemotherapy. Additionally, platinum agents might enhance immune responses by boosting antigen presentation and promoting immunogenic cell death. This systematic review assesses if the combination of platinum and immunotherapy is more effective than using platinum alone in TNBC [14],[15].

Outcomes Assessed

- Pathological complete response (pCR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Event-free survival (EFS)
- Objective response rate (ORR)
- Toxicity profile

Biological Rationale for Platinum Plus Immunotherapy

Platinum Sensitivity in TNBC

Platinum compounds generate DNA cross-links, leading to apoptosis. DNA repair deficiency in TNBC is often characterized by: mutations in BRCA1, mutations in BRCA2, and alterations in PALB2, Homologous recombination deficiency (HRD). Therefore, TNBC is intrinsically sensitive to platinum therapy [2], [4]. [6].

Immunogenic Features of TNBC

Compared with hormone receptor-positive breast cancers, TNBC demonstrates:

- Increased stromal lymphocytic infiltration
- PD-L1 expression on tumor and immune cells
- Higher mutational load
- More inflamed tumor microenvironment [7], [8]. [13]

Synergy between Platinum and Immunotherapy

Platinum chemotherapy may:

- Release tumor neoantigens
- Enhance dendritic cell maturation
- Promote T-cell priming
- Reduce myeloid suppressor cells
- Increase PD-L1 expression

Thus, checkpoint inhibition may sustain immune-mediated tumor cell death after chemotherapy-induced antigen release [13], [15].

Platinum Alone in TNBC: Historical Perspective

Platinum agents were extensively studied in TNBC before the immunotherapy era.

Metastatic Setting

Single-agent or combination carboplatin/cisplatin demonstrated response rates ranging from 20 to 40%, especially in BRCA-mutated tumors [4], [6].

Neoadjuvant Setting

Trials such as:

- CALGB 40603
- GeparSixto
- BrighTNess

They showed improved pathological complete response when carboplatin was added to standard neoadjuvant chemotherapy. However, toxicity especially hematologic toxicity, increased substantially.

Although platinum improved pCR, the survival benefit remained inconsistent across earlier trials [4], [6], [20].

Platinum Plus Immunotherapy in Metastatic TNBC

KEYNOTE-355

This landmark phase III trial evaluated pembrolizumab plus chemotherapy (taxane or gemcitabine/carboplatin) versus placebo plus chemotherapy in patients with previously untreated locally recurrent inoperable or metastatic TNBC.

Key Findings:

- Significant improvement in PFS in PD-L1 CPS ≥10 population
- OS benefit later confirmed
- Greatest benefit observed in PD-L1 positive disease
- Manageable safety profile

This trial established pembrolizumab plus chemotherapy as the standard first-line treatment for PD-L1 positive metastatic TNBC [7], [17].

IMpassion130

This phase III trial compared atezolizumab plus nab-paclitaxel with placebo plus nab-paclitaxel.

Findings:

- Improved PFS in intention-to-treat population
- Clinically meaningful OS benefit in PD-L1 positive subgroup
- Durable responses observed

This was the first positive immunotherapy trial for breast cancer [8].

IMpassion131

Atezolizumab plus paclitaxel failed to improve PFS or OS compared to paclitaxel alone.

Clinical Implications:

- Choice of chemotherapy backbone matters
- Corticosteroid premedication with paclitaxel may affect immunotherapy efficacy
- Nab-paclitaxel may be more favorable partner [15].

Platinum Plus Immunotherapy in Early TNBC

KEYNOTE-522

One of the most practice-changing neoadjuvant trials.

Regimen:

- Pembrolizumab + carboplatin + paclitaxel
- Followed by anthracycline/cyclophosphamide
- Then adjuvant pembrolizumab

Results:

- Significantly higher pCR
- Improved event-free survival
- Benefit seen irrespective of PD-L1 status
- Greater benefit in node-positive/high-risk patients [9], [16].

IMpassion031

Atezolizumab combined with neoadjuvant chemotherapy significantly improved pCR compared to placebo [10].

GeparNuevo

Durvalumab, when added to neoadjuvant chemotherapy, improved long-term outcomes and immune activation signatures [11].

NeoTRIPaPDL1

Did not significantly improve pCR, although event outcomes suggested possible later benefits [13].

Comparative Analysis: Platinum Plus Immunotherapy vs Platinum Alone [4], [7], [14].

Parameter	Platinum Alone	Platinum + Immunotherapy
Pathological Complete Response	Moderate	Higher
Progression-Free Survival	Standard	Improved
Overall Survival	Limited benefit	Better in selected patients
Event-Free Survival	Lower	Improved
Response Durability	Shorter	Longer
Biomarker Dependence	BRCA/HRD	PD-L1/TILs/immune markers
Toxicity	Hematologic, renal, neuropathy	Hematologic + immune toxicity

Biomarkers for Treatment Selection

PD-L1 Expression

Most validated biomarker for metastatic TNBC.

- CPS ≥10 strongly predicts pembrolizumab benefit.

BRCA Mutation / HRD

It may predict platinum sensitivity.

Tumor Infiltrating Lymphocytes

High TILs are associated with:

- Better prognosis
- Greater immunotherapy responsiveness

Emerging Biomarkers

- ctDNA clearance
- Gene expression signatures
- Tumor mutational burden
- Microbiome associations

Safety and Tolerability

Platinum Toxicities

- Neutropenia
- Anemia
- Thrombocytopenia
- Neuropathy
- Nephrotoxicity (cisplatin)
- Ototoxicity
- Nausea/vomiting

Added Immunotherapy Toxicities

- Hypothyroidism
- Hyperthyroidism
- Hepatitis
- Colitis
- Pneumonitis
- Skin rash
- Adrenal insufficiency
- Type 1 diabetes (rare)

Clinical Management

- Early recognition essential
- Corticosteroids for grade ≥2 irAEs
- Endocrine replacement therapy if permanent damage

DISCUSSION

Evidence strongly supports the combination of immunotherapy with platinum-based chemotherapy in TNBC. In metastatic disease, benefit is concentrated in PD-L1 positive patients. In early-stage disease, the benefit extends more broadly, particularly for stage II–III tumors.

Platinum alone remains relevant in:

- Patients ineligible for immunotherapy

- Autoimmune disorders
- Organ transplant recipients
- Resource-limited settings
- PD-L1 negative metastatic TNBC

However, immunotherapy combinations are increasingly becoming the standard of care where available [7],[9],[10],[16] .

Limitations of Available Evidence

- Different PD-L1 assays across trials
- Variable chemotherapy backbones
- Inconsistent platinum dosing schedules
- Limited long-term OS data in early-stage disease
- Cost and access barriers globally[7],[8],[13].

Future Directions

- Personalized biomarker-driven therapy
- Combining PARP inhibitors + platinum + immunotherapy
- De-escalation strategies for responders
- Novel immune combinations (TIGIT, LAG-3, vaccines)
- ctDNA-guided adjuvant decisions [13],15].

CONCLUSION

Platinum plus immunotherapy is superior to platinum alone for many patients with TNBC, particularly those with:

- PD-L1 positive metastatic disease
- Stage II–III early TNBC receiving neoadjuvant therapy [9],[16].

The combination improved pCR, PFS, EFS, and OS but increased immune-related adverse events. Future treatment selection should integrate biomarkers, patient comorbidities, and access considerations [13],[15].

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