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REVIEW ARTICLE

Advances in platinum-based cancer therapy: overcoming platinum resistance through rational combinatorial strategies

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Abstract

Platinum-based cancer therapy remains a cornerstone of first-line treatment for several solid tumours such as ovarian, testicular, and non-small cell lung cancers, where it has received regulatory approval as both monotherapy and combination regimens. However, the inevitable emergence of resistance has necessitated extensive preclinical and clinical efforts to develop rational platinum-based combinations. The most appealing candidates for combination therapy are those that offer additive and/or synergistic effects without undesirable overlapping toxicities. Whilst early strategies focussed on co-administration with cytotoxic chemotherapies, recent advances have shifted towards combinations with targeted therapies and immunotherapies, offering improved efficacy and durability of response. In this review, we provide a comprehensive analysis of recent clinical trials evaluating platinum-based combination strategies (excluding radiotherapy) and give an overview of trial concepts that will lead to more refined therapies for cancer. We also highlight emerging dual-drug codelivery nanosystems, platinum-based antibody–drug conjugates (ADCs), and multi-targeted platinum compounds with promising preclinical and/or clinical evidence. Beyond traditional drug pairings, the improved design strategies of new platinum compounds such as their incorporation into ADCs offer enhanced targeting and reactivity. Whilst promising preclinical examples like trastuzumab-Pt(II) and cetuximab-C8Pt(IV) bring optimism to combinatorial approaches, significant challenges including stability and controlled payload release remain to be addressed before clinical translation. By integrating advances in molecular profiling and rational drug development, platinum-based therapies continue to evolve, offering renewed optimism for overcoming drug resistance and improving patient outcomes, although challenges such as biomarker identification, toxicity management, and treatment costs remain to be fully addressed.

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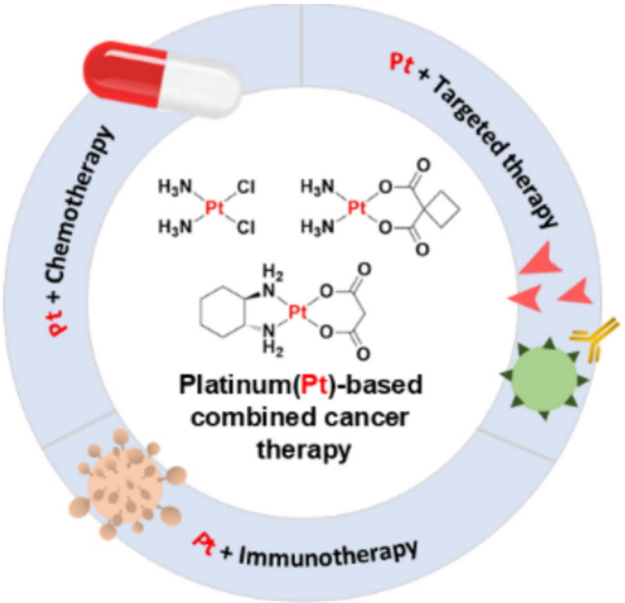
Graphical abstract



Keywords Platinum · Platinum resistance · Cancer · Combination therapy · Drug synergy

Introduction

Cancer remains a burden on society due to its high mortality and morbidity, as well as the economic strain it places on healthcare systems [1, 2]. Amongst the established chemotherapeutic agents, metallodrugs have been extensively used for cancer therapy where they offer versatile electronic and unique structural features [3–5]. The tuning of the metal,

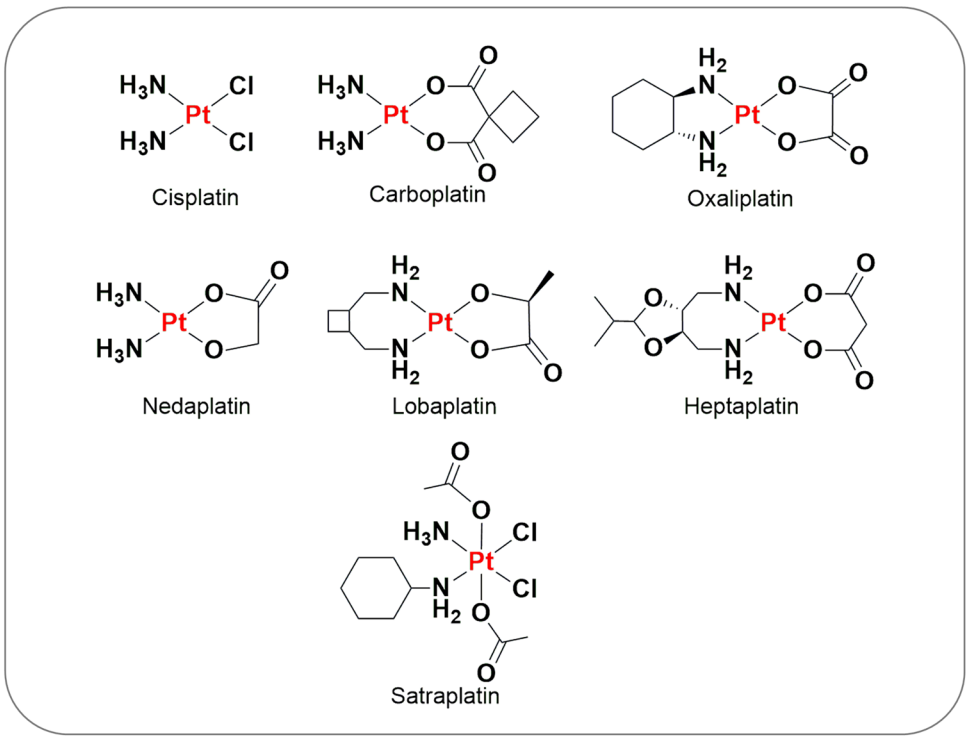


Fig. 1 Clinical and FDA-approved anti-cancer platinum-based metallodrugs

ligand, or metal–ligand interaction provides exceptional structural diversity and novel chemistry for drug design, resulting in a greater range of functions and unique mechanisms of action. In contrast to organic drugs, metallodrugs are often 'prodrugs' that convert into active forms once they enter the body or when they reach the desired target. This activation frequently involves the displacement or dissociation of one or more labile ligands, the opening of chelate rings, or a change in the oxidation state of the metal and/or ligands. Additionally, metallodrugs can also be selectively activated by external stimuli such as light, radiation, ultrasound, or heat upon reaching the target site. The antiproliferative effects of cisplatin (cis-diamminedichloroplatinum(II)) (Fig. 1) were discovered in 1965 by Barnett Rosenberg with the aid of serendipity, where his group observed that the inhibition of bacterial growth was not caused by electric fields, but rather by the platinum (Pt) compound that was released from the electrodes [6]. In 1978, the FDA granted regulatory approval for cisplatin to be used for the treatment of a variety of solid malignancies, making it one of the most successful therapeutic metallodrugs to date [6, 7]. Cisplatin exerts its cytotoxic effects through a complex interplay of molecular mechanisms, primarily by coordinating DNA to form platinum–DNA adducts, resulting in DNA damage, mitochondrial dysfunction, reactive oxygen species (ROS) generation, modulation of cell death pathways and subsequent apoptosis [7]. These multifaceted effects underscore the potency of cisplatin as a chemotherapy agent. However, despite being effective in numerous cases, cisplatin is linked to significant off-target toxicity, including nephrotoxicity, ototoxicity, and neurotoxicity [8]. Also, constant or prolonged cisplatin treatment often results in the acquisition of resistance through the selection bias of alternative cell survival pathways, leading to therapeutic failure and poor prognosis [9, 10].

Given the early success of cisplatin and to overcome its drawbacks, second- and third-generation cisplatin analogues were developed. One of the most successful platinum analogues is carboplatin (cis-diammine(1,1-cyclobutanedicarboxylato) platinum(II)) (Fig. 1) which was reported by Cleare and Hoeschele in 1973, and then gained FDA approval in 1989 [11]. Shortly after this, oxaliplatin (1R,2R-diaminocyclohexane oxalatoplatinum(II)) (Fig. 1) received European approval in 1999 and FDA approval in 2002 [12]. These second-generation platinum-based metallodrugs were developed with specific goals such as reducing toxicity, improving stability, and broadening the range of activity compared to cisplatin. Other drugs of a similar design were subsequently developed including nedaplatin, lobaplatin, and heptaplatin (Fig. 1), which have each gained approval in Japan, China, and South Korea, respectively [13]. Other than these drugs, satraplatin (Fig. 1) was developed, exciting great interest due to its high oral availability such that it can be administered in pill form, greatly improving patient convenience and reducing health care costs [14, 15]. Satraplatin has proven that overcoming the initially limiting conditions for platinum drug design (platinum(II) and cis-conformation) will help fuel the design of new lead compounds with improved functionality.

Anti-cancer monotherapies, whether broadly active cytotoxics or even the most effective molecularly targeted drugs, have limited ability to induce long-lasting clinical responses, as drug resistance is common [16]. Moreover, single-drug therapy is typically inadequate for patients with advanced disease, leading to rapid disease progression and poor clinical outcomes [17]. As a result, combination therapies of two or more drugs now dominate modern cancer medicine. Specifically, additive and/or synergistic relationships can convert less effective single-drug treatments into regimens with robust anti-tumour activity [17]. Drug synergy is achieved when the combined effect of two or more drugs is greater than that predicted by their individual potencies where this has the advantages of: (1) increasing drug efficacy; (2) significantly lower therapeutic doses for each individual drug compared to when they are administered alone; (3) minimising the development of drug resistance or relapse; (4) achieving high cancer selectivity (cancer cell killing without affecting normal cells); and (5) expanding the range of treatment-responsive cancers [18, 19]. Many reviews have provided comprehensive perspectives on the use of platinum metallodrugs given as monotherapies [20, 21]. In this review, we specifically focus on the use of these platinum metallodrugs in combinatorial therapy to treat various cancers, considering the potential benefits compared to the risks in such approaches. We present examples of investigations into such combinations, with a significant emphasis on recent clinical studies, the majority of which have been completed since 2019. The primary endpoints of these clinical trials were highlighted, and the available clinical data is reported in Supplementary Table S1. Current and completed trials have examined platinum drugs with various therapies, including cytotoxic agents (37%), targeted therapies (44%), and immunotherapies (18%) (Fig. 2).

Platinum/cytotoxic combinations

Established platinum/cytotoxic combinations

Given the mounting clinical evidence, platinum-based doublet chemotherapy regimens have gained FDA approval and become the standard first-line treatment for specific cancers, including ovarian and non-small cell lung cancers (NSCLC), reflecting their demonstrated clinical efficacy. However, their use is not universal across all cancer types, such as prostate or breast cancer, where other therapeutic

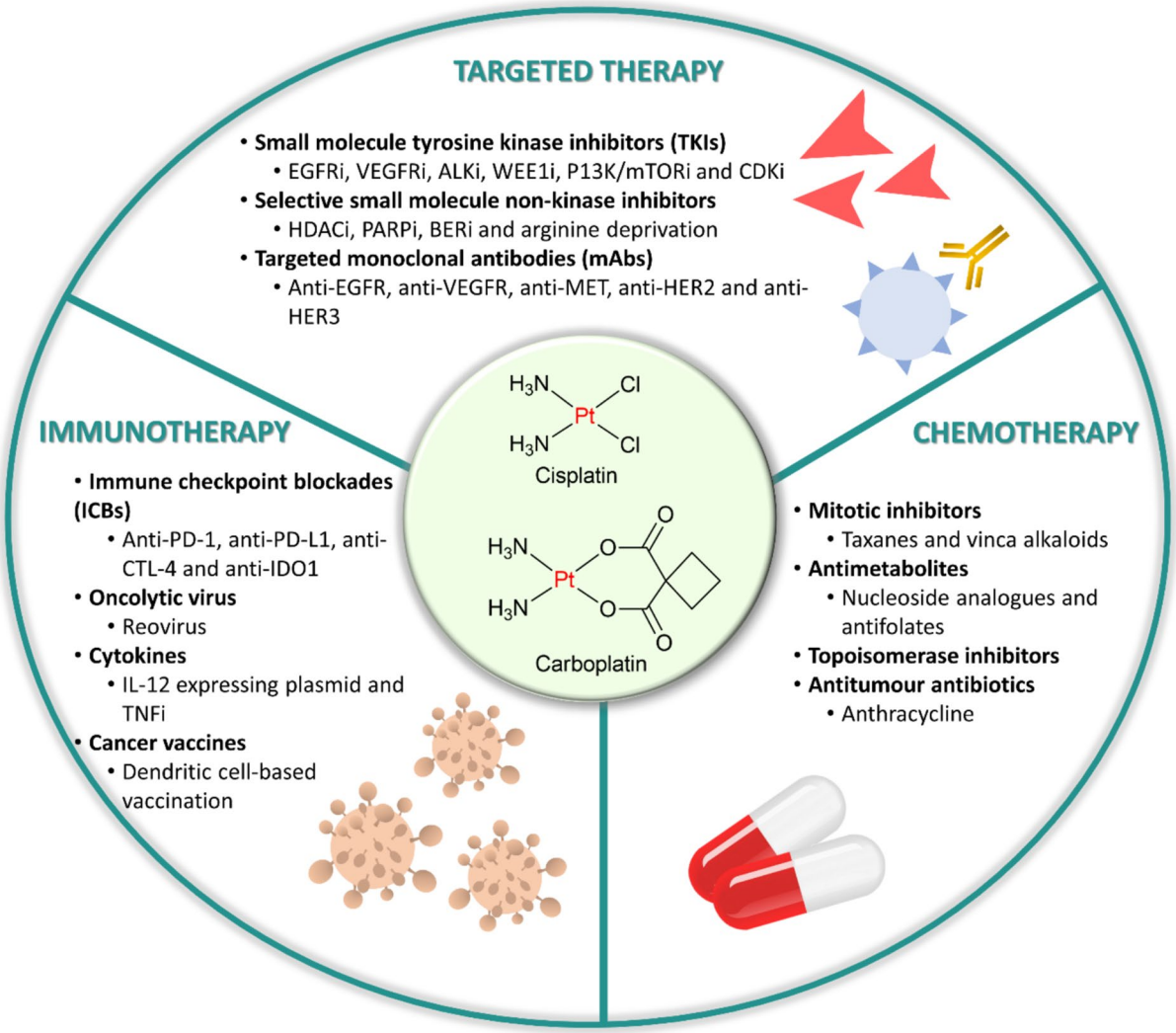


Fig. 2 Combination strategies of platinum-based drugs (cisplatin or carboplatin) with various therapies have been explored extensively, with cytotoxic agents accounting for 37% of combinations, targeted therapies representing 44%, and immunotherapies comprising 18%. These approaches aim to enhance the therapeutic efficacy of platinum-based chemotherapy by leveraging different mechanisms of action. Cytotoxic agents, such as taxanes and antimetabolites, amplify DNA damage and impair tumour cell repair processes. Targeted therapies, including tyrosine kinase inhibitors and monoclonal antibodies (mAbs), selectively enhance the vulnerability of cancer cells to platinum drugs. Immunotherapies, particularly immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4, further potentiate the anticancer response by modulating the tumour microenvironment

strategies are preferred. Notably, paclitaxel (taxane), in combination with either cisplatin or carboplatin, was approved by FDA for treating patients with advanced ovarian cancer after initial surgery [22], and NSCLC [23, 24]. Due to the success of this regimen, the platinum/cytotoxic combinations have been examined in current clinical settings for various advanced cancers. In an intriguing approach, a phase I study has investigated the combination of carboplatin with paclitaxel injection concentrate for nano-dispersion (PICN) in patients with advanced solid malignancies (ClinicalTrials.gov Identifier: NCT01304303) [25]. These nanoformulations offer the advantage of a wider therapeutic window and reduced toxicity. Due to observed efficacy in part A of the study, an early efficacy assessment of this treatment was also conducted in patients with unresectable biliary tract cancers (BTCs). Notably, this study demonstrated that PICN either alone or in combination with carboplatin was safe and had stable pharmacokinetics, thereby warranting further phase II trials. Pegylated liposomal doxorubicin (PLD) is doxorubicin encapsulated within a sterically stabilised liposome. Delivery using this pegylated liposomal carrier increases the circulating half-life of doxorubicin from approximately 3–55 h, whilst reducing cardiac toxicity and myelosuppression compared to conventional doxorubicin

[26]. Consequently, the combinations of doxorubicin or PLD with platinum drugs have been explored in phase II/III clinical studies (NCT02413320 and NCT00538603) [27, 28]. Results from the phase III trial, which evaluated the carboplatin/PLD combination in patients with partially platinum-sensitive ovarian cancer, demonstrated a prolonged median progression-free survival (mPFS) compared to those treated with carboplatin/paclitaxel (11.3 vs. 9.4 months; $P = 0.005$, stratified log-rank test) [28]. Notably, the carboplatin/PLD regimen also showed more favourable risk–benefit profile than the standard carboplatin/paclitaxel suggesting its potential as an alternative to standard therapy for ovarian cancer patients. Recently, acelarin, a phosphoramidate transformation of gemcitabine, was developed to improve upon the limitations of gemcitabine (a nucleoside analogue), including stability, uptake, and resistance issues, potentially offering enhanced efficacy and an improved therapeutic profile. To date, acelarin remains an investigational agent and is not currently FDA-approved or in routine clinical use. Interestingly, it was evaluated in combination with cisplatin in a phase Ib clinical trial in patients with locally advanced or metastatic BTC (NCT02351765) [29]. This combination demonstrated an objective response rate (ORR) of 33%, a mPFS of 7.2 months and a median overall survival (mOS) of 9.6 months, comparable to outcomes achieved with standard cisplatin/gemcitabine treatment.

Subsequent studies have investigated the potential of a three-drug combination, for instance, cisplatin/gemcitabine/S-1 (an oral fluoropyrimidine) in patients with advanced BTC (NCT02182778) [30]. This study reported modest but statistically significant improvements in mOS (13.5 vs. 12.6 months; $P = 0.046$, stratified log-rank test), mPFS (7.4 vs. 5.5 months; $P = 0.015$), and response rate (RR, 41.5% vs. 15%) for the cisplatin/gemcitabine/S-1 (CGS) regimen compared to cisplatin/gemcitabine (CG). Although the absolute gains were limited, the findings suggest a potential clinical benefit of the CGS regimen, warranting further investigation in specific patient subgroups. A four-drug combination of cisplatin/docetaxel/gemcitabine/capecitabine was assessed in patients with metastatic pancreatic cancer (NCT01459614), where this regimen demonstrated survival benefit and was safe and well tolerated [31]. For this reason, a subsequent study was conducted to examine the addition of irinotecan to the cisplatin/gemcitabine/docetaxel/capecitabine regimen in patients with metastatic pancreatic cancer (NCT02324543) [31, 32]. Although the study did not achieve its primary endpoints, the treatment regimen was generally safe and well tolerated, indicating that additional refinement may be beneficial. The study reported that the most common grade 3 or higher treatment-related adverse events were anaemia (60%), neutropenia (60%), and leukopenia (47%), with no treatment-related deaths reported. Although these combinations using multiple drugs simultaneously may not directly target platinum resistance mechanisms, they have the potential to increase efficacy and delay the development of resistance when compared to platinum monotherapy. For example, a study by Shroff et al. demonstrated that the combination of cisplatin with nab-paclitaxel/gemcitabine resulted in improved clinical outcomes, including mOS of 19.2 months and a mPFS of 11.8 months in patients with advanced BTC (NCT02392637) [33], indicating enhanced efficacy and potential to mitigate resistance.

Overlapping toxicity

Despite emerging evidence of augmented anti-tumour activity from platinum/cytotoxic combinations, their use is often hindered by unacceptable overlapping toxicity. This caution arises from the recognised side effects of platinum drugs, particularly when combined with other chemotherapy agents that target rapidly dividing cells, such as taxanes. For instance, in a randomised phase III trial, carboplatin/paclitaxel combination showed clinical benefits but was associated with significant toxicities, including grade 3/4 neutropenia (50%), grade 2 alopecia (86%), neuropathy and hypersensitivity reactions [34]. Although the combination of carboplatin and amrubicin (a topoisomerase inhibitor) demonstrated clinical benefits in patients with extensive-stage small cell lung cancer (SCLC) (NCT01076504) [35], no increased efficacy compared to standard treatments was observed, and severe myelosuppression was noted. Despite the fact that certain platinum/cytotoxic combinations are associated with notable toxicities, including high-grade adverse events in some cases (e.g. carboplatin/paclitaxel-induced grade 3/4 neutropenia in approximately 50% of patients), many regimens have also demonstrated enhanced clinical benefits compared to monotherapy, with manageable or acceptable safety profiles in specific patient populations. For instance, a platinum/docetaxel combination achieved a pathologic complete response (pCR) rate of 52% with a favourable toxicity profile in triple-negative breast cancer (TNBC) patients (NCT02413320) [27]. Similarly, cisplatin combined with the vinca alkaloid vinorelbine has shown efficacy and tolerability as a first-line therapy in NSCLC patients, with an OS of 10.2 months and an acceptable safety profile (EudraCT number: 2012–003531-40) [36]. The variability in observed toxicity across studies can be attributed to differences in patient characteristics, treatment regimens, supportive care measures, and study designs [37, 38]. These findings highlight the importance of personalised treatment approaches that balance efficacy with the risk of toxicity, along with careful monitoring and supportive care to mitigate adverse effects.

Combining platinum-based drugs with targeted therapies

Molecularly targeted small molecule drugs represent a cornerstone in cancer treatment due to their greater specificity and safety (more tumour-selective) compared to traditional chemotherapy [39]. Since the FDA approved the first tyrosine kinase inhibitor (TKI), imatinib, in 2001, numerous small molecule targeted drugs have been introduced into clinical oncology [40]. Of note, recent advancements in understanding the diverse mechanisms of platinum drugs, beyond inducing DNA damage, have facilitated the rational design of combination therapies with specific inhibitors (Fig. 3). This strategy, leveraging the complementary effects of diverse drugs, seeks to enhance anti-tumour efficacy and patient outcomes. Combination therapies that use drugs with distinct mechanisms are promising, as they can bypass resistance to both drugs.

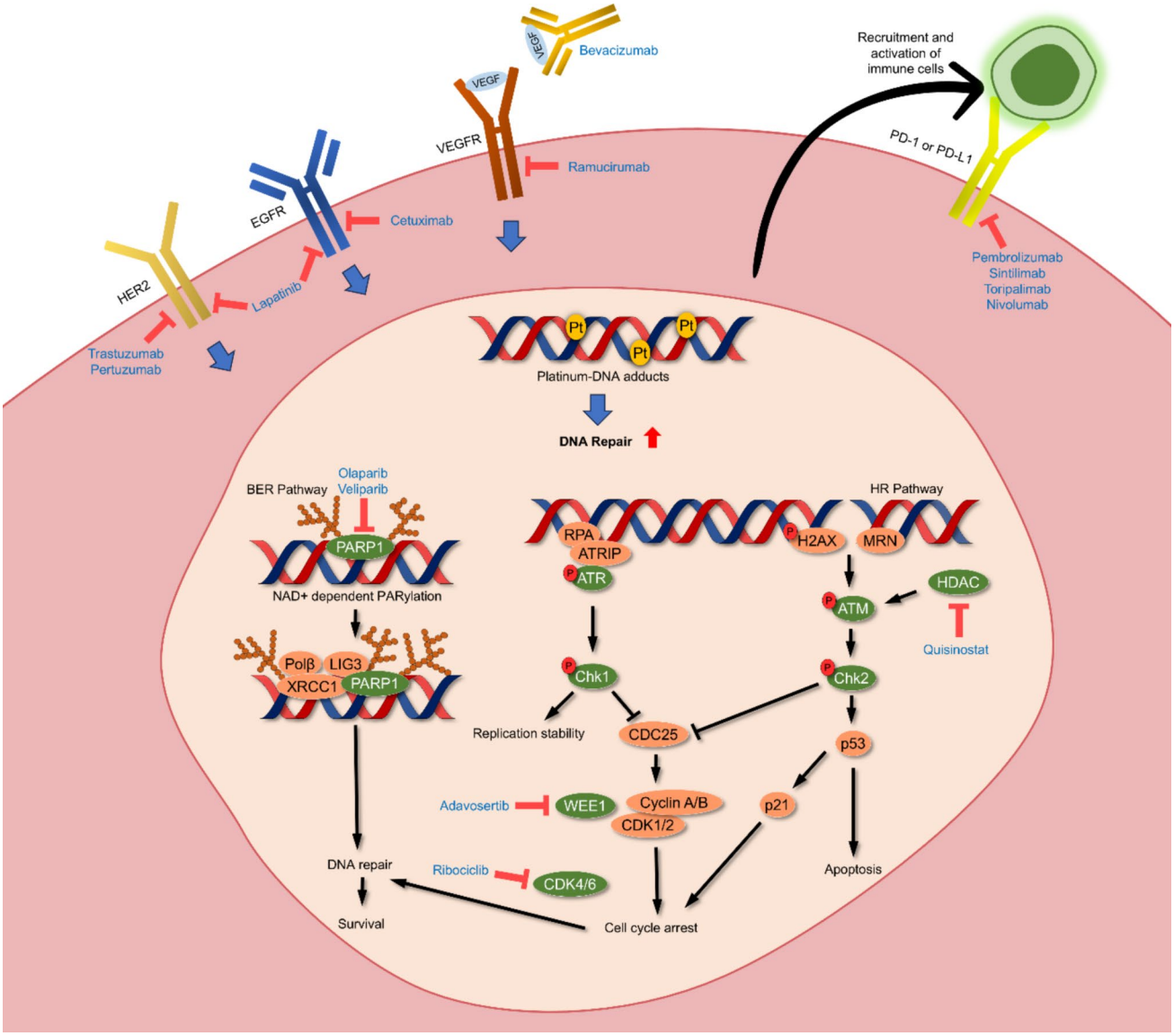


Fig. 3 Targets for combinations with platinum-based chemotherapy. This figure illustrates key pathways that influence the response to DNA damage and are targeted in combination with platinum-based chemotherapy. These include DNA damage response (DDR) pathways such as homologous recombination (HR) and non-homologous end joining (NHEJ), which are targeted by PARP and ATM/ATR inhibitors. Additionally, cell cycle regulators such as CDK inhibitors play crucial roles in sensitising tumours to platinum therapy. Immune-related mechanisms, including checkpoint inhibitors targeting PD-1/PD-L1, enhance anti-tumour immune responses in combination with platinum drugs and overcome resistance mechanisms

Tyrosine kinase inhibitors (TKIs)

Tyrosine kinases play a pivotal role in initiating intracellular signal-transduction cascades that regulate cell proliferation and survival. Given their overexpression in various cancers, inhibiting these kinases offers a targeted therapeutic approach [41]. A notable example of tyrosine kinase inhibitors (TKIs) are the WEE1 inhibitors, which regulate the G2/M transition and maintain genomic stability [42]. Inhibiting WEE1 induces premature mitosis entry, leading to mitotic catastrophe. Preclinical studies have shown that adavosertib, a potent and selective WEE1 inhibitor, enhances the efficacy of platinum chemotherapy, particularly in tumour protein p53 (TP53)-deficient tumours models [43]. This was evidenced in a phase II trial where adavosertib combined with carboplatin/paclitaxel showed clinical benefit in women with platinum-sensitive TP53-mutant ovarian cancer (NCT01357161). The combination resulted in improved mPFS compared to placebo [7.9 vs. 7.3 months; two-sided $P = 0.080$, exceeding the established significance threshold ($P < 0.2$)] [44], although it is important to note that TP53 mutation does not always equate to functional deficiency. Targeted therapies are developed to impede critical pathways implicated in tumour growth and metastasis. However, some tumours may evade treatment by using alternative pathways, necessitating a multi-targeted strategy to combat resistance [45, 46].

Selective small molecule non-kinase inhibitors

Small molecule non-kinase inhibitors selectively bind to targets outside the kinome, effectively inhibiting downstream signalling pathways. This class of drugs includes poly(ADP-ribose) polymerase (PARP) inhibitors that have received FDA approval [47, 48]. Prominent examples of PARP inhibitors (PARPi) include olaparib, niraparib, rucaparib, talazoparib, and veliparib. Mechanistic studies indicate that platinum/PARPi synergy is associated with sustained DNA double-strand breaks (DSBs) leading to a significantly marked increase in apoptosis [49, 50]. These preclinical data have prompted clinical trials to assess this combination in various advanced cancers including TNBC, ovarian, SCLC and head and neck squamous cell carcinoma (HNSCC) (NCT01074970, NCT01063816, NCT02032277, NCT01642251, NCT01711541, NCT02163694, and NCT03150576) [51–58]. Encouragingly, in patients with extensive-stage SCLC, the addition of veliparib to a cisplatin/etoposide regimen met its primary endpoint with improved mOS (10.2 vs. 8.9 months; one-sided $P = 0.17$) and ORR (71.9% vs. 65.6%; two-sided $P = 0.57$) compared to a placebo-treated group [55]. In addition, combining veliparib with a carboplatin/paclitaxel regimen was found to be well tolerated in advanced HNSCC patients, with 2-year OS rate of 77.8% and 2-year PFS rate of 66.7% [56]. Notably, in a double-blind phase III trial, the subgroup analysis showed that the addition of veliparib to a carboplatin/paclitaxel regimen resulted in durable benefit with prolonged mPFS compared to the placebo/chemotherapy arm for all subgroups defined by homologous recombination (HR) or breast cancer susceptibility genes (BRCA1/2) status (HR +: 13.0 vs. 12.5 months, $P = 0.013$; TNBC: 16.6 vs. 14.1 months, $P = 0.052$; germline mutation in BRCA1 (gBRCA1): 14.2 vs. 12.6 months, $P = 0.073$; and gBRCA2: 14.6 vs. 12.6 months, $P = 0.021$) [57]. Importantly, the efficacy of PARPi in combination with platinum drugs also depends on the HR repair capacity of the tumours. In BRCA-deficient tumours—where HR is impaired—PARP inhibition leads to synthetic lethality, thereby improving therapeutic outcomes. In contrast, BRCA-proficient or HR-competent tumours may derive limited benefit from this strategy. For instance, the PARTNER trial reported no added benefit of olaparib when combined with neoadjuvant carboplatin/paclitaxel in BRCA-proficient TNBC, showing no improvement in pCR, event-free survival (EFS), or OS [58]. This contrasts sharply with the significant benefits observed in BRCA-deficient TNBC patients, as reported in an analysis within the PARTNER trial [59]. These findings highlight the critical role of BRCA mutation status and HRD as predictive biomarkers for PARP inhibitor efficacy and reinforce the need for biomarker-guided treatment selection. Furthermore, due to their complementary mechanisms of action, the combined use of methoxyamine, a base excision repair (BER) inhibitor, with cisplatin/pemetrexed has shown promising anti-tumour effects, notably in salivary gland tumours, whilst maintaining a tolerable safety profile at the tested doses (NCT02535312) [60].

Targeted monoclonal antibodies (mAbs)

Monoclonal antibodies (mAbs) are engineered proteins designed to target the extracellular domains of specific antigens. Through this targeting, they disrupt ligand binding, impede subsequent activation, and block downstream signalling pathways involved in cancer cell growth and survival. For instance, the anti-epidermal growth factor receptor (EGFR) mAb cetuximab inhibits EGFR signalling, which can indirectly enhance the efficacy of DNA-damaging platinum drugs and improve their anti-tumour activity [61]. This combination is particularly effective in cancers with overexpressed or mutated EGFR. For this reason, cetuximab in combination with platinum-based regimens was evaluated in phase II/III trials (NCT01437449 and NCT02268695) [62, 63]. Subsequently, antibodies that target VEGF, also known as anti-angiogenesis agents, such as bevacizumab and ramucirumab, had undergone clinical investigations to determine their suitability as partners for platinum-based regimens (NCT00989651, NCT01160744, NCT01735071,

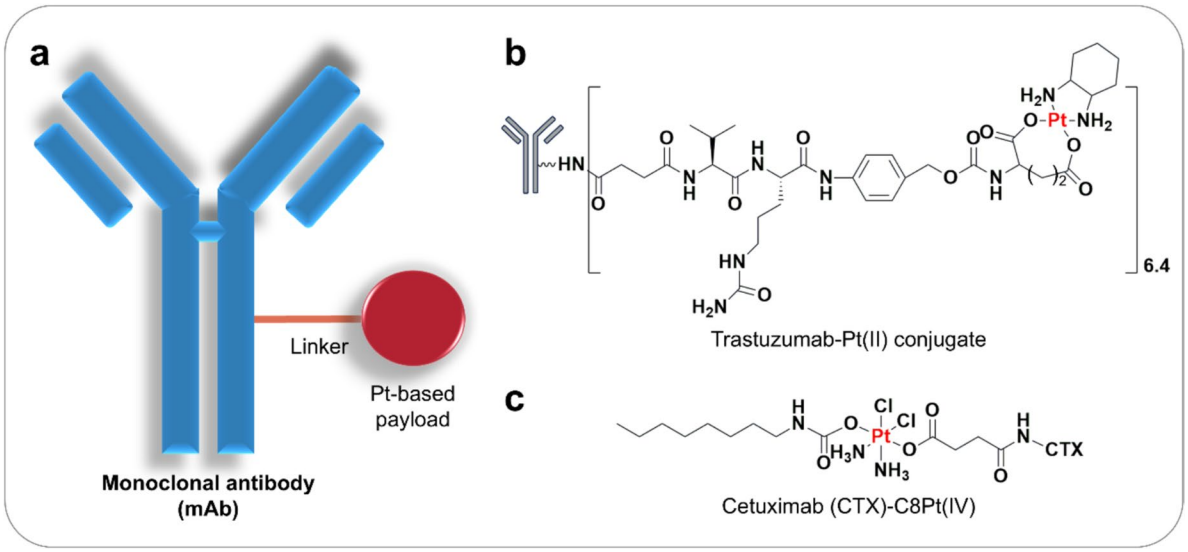


Fig. 4 Platinum-based antibody–drug conjugate (ADC) as new strategies for specific tumour-targeting. **a** Platinum compounds are conjugated with monoclonal antibodies (mAbs) to enhance drug delivery and targeting. **b** Structure of trastuzumab-Pt(II) conjugate. **c** Structure of cetuximab-C8Pt(IV)

NCT02359058, and NCT02363751) [64–67]. By inhibiting angiogenesis, these mAbs reduce the nutrient and oxygen supply to tumours and impair their ability to repair DNA damage, making them more susceptible to platinum-induced DNA damage. The addition of bevacizumab or ramucirumab to platinum-based regimens did not reveal any new or unexpected safety concerns, but neither were overall outcomes improved compared to standard platinum-based regimens, suggesting further optimisation is warranted.

Human epidermal growth factor receptor 2 (HER2) promotes cell growth and division, and is frequently overexpressed in various cancers, notably ovarian and breast carcinomas [68]. Trastuzumab and pertuzumab function by blocking HER2 signalling, thereby disrupting tumour cell proliferation. Thus, combining these anti-HER2 agents with DNA-damaging platinum drugs may enhance cancer cell death, specifically benefiting individuals with HER2-positive cancers. These combinations have been evaluated across various cancers, including urinary tract, gastric, breast, and gastroesophageal junction cancer (NCT00515411, NCT01358877, and NCT02205047) [69–71]. The addition of trastuzumab to platinum-based regimens was found to be effective and safe in patients with metastatic HER2-positive gastric cancer (ORR: 65%, mPFS: 13 months, and mOS: 24.9 months) [69]. Similarly, adding pertuzumab to trastuzumab and platinum-based chemotherapy conferred clinical benefits in patients with HER2-positive breast cancer [70].

Overall, mAbs have demonstrated encouraging clinical benefits when added to platinum regimens in various studies, albeit with some variability in results. Unlike TKIs, mAbs typically exhibit high specificity for their targets, which can result in variable outcomes influenced by factors such as tumour heterogeneity and patient selection criteria. Consequently, the development of mAbs may require careful selection of cancer types, stages, and suitable combination partners to ensure improved clinical outcomes. Nonetheless, these examples underscore how understanding the mechanisms of action of platinum drugs has facilitated the development of more effective combination therapies with targeted agents like mAbs. The key contribution of platinum-based drugs lies in their ability to induce DNA damage, which, when combined with the targeted inhibition of growth and survival pathways by mAbs, leads to enhanced anti-tumour efficacy.

Platinum-based antibody–drug conjugates (ADCs)

The advent of antibody–drug conjugate (ADC) has revolutionised cancer therapy by precisely targeting tumour antigens, improving efficacy, reducing drug toxicity, and enhancing the therapeutic window. Thanks to the advances in synthetic chemistry, ADCs have been designed to comprise tumour-targeting mAbs linked to cytotoxic payloads via intricately designed chemical linkers, simultaneously enabling potent effectiveness and precise targeting, thereby expanding the therapeutic index [72]. Mirvetuximab soravtansine is an example of an ADC where the antibody mirvetuximab (anti-folate receptor α, or anti-FRα) is linked to a cytotoxic drug called DM4 (a maytansinoid). In an intriguing approach, carboplatin was examined in combination with mirvetuximab soravtansine in patients with platinum-sensitive ovarian cancer in a phase Ib trial

(NCT02606305) [73]. This combination demonstrated clinical benefit and is well tolerated (ORR: 71% and mPFS: 15 months). Whilst most ADCs in the preclinical and clinical developments rely on complex organic molecules, the potential of conjugating metallodrugs to mAbs has been largely neglected. Metallo-based ADCs might reduce the high cost associated with producing targeted chemotherapeutics, as their bioconjugation to mAbs could be simpler compared to cytotoxic payloads derived from organic molecules and natural products (Fig. 4a) [74]. Studies have shown that the conjugation of platinum drugs to trastuzumab via a cathepsin B cleavable dipeptide enhances drug accumulation and enables specific delivery to HER2-positive cancer cells (Fig. 4b) [75]. Trastuzumab-Pt(II) conjugate has been loaded with approximately 6.4 mol of platinum drugs per mole of antibody, retaining a high and selective binding affinity for the HER2 protein and HER2-positive SK-BR-3 breast cancer cells. Compared to oxaliplatin, trastuzumab-Pt(II) conjugate exhibits a higher cellular uptake of platinum drugs with improved in vitro cytotoxicity against SK-BR-3 cells. Similarly, conjugation of a new cytotoxic platinum (IV) prodrug (C8Pt(IV)) with cetuximab (Cet-C8Pt(IV)) also showed excellent tumour targeting in cutaneous squamous cell carcinoma (Fig. 4c) [76].

Compared to free platinum drugs, antibody-platinum (Ab-Pt) conjugates exhibit distinct cellular uptake mechanisms, platinum accumulation profiles, and DNA platination efficiency. Free platinum drugs such as cisplatin and oxaliplatin primarily enter cells via passive diffusion, leading to relatively non-specific intracellular distribution. In contrast, Ab-Pt conjugates are internalised via receptor-mediated endocytosis, enabling more targeted delivery to tumour cells. Experimental studies demonstrate the advantages of this approach. In HER2-positive SK-BR-3 cells, free oxaliplatin showed faster initial uptake, reaching 25 ng Pt per million cells at 4 h, approximately 1.7-fold higher than Herceptin-Pt(II) conjugate [75]. However, after 24 h, platinum accumulation in Herceptin-Pt(II)-treated cells reached 224 ng Pt per million cells, compared to only 67 ng for oxaliplatin-treated cells. This difference highlights the enhanced and sustained cellular uptake conferred by antibody targeting, attributed to the specific interaction between Herceptin and HER2 receptors and subsequent receptor-mediated endocytosis. Similarly, in EGFR-positive epidermoid carcinoma A-431 cells, treatment with a cetuximab-conjugated platinum(IV) prodrug (Cet-C8Pt(IV)) resulted in platinum concentrations 6.83 and 6.58 times higher than free C8Pt(IV) and a non-conjugated C8Pt(IV)/cetuximab mixture, respectively [76]. Competitive inhibition experiments confirmed that Cet-C8Pt(IV) targets EGFR specifically, as platinum uptake was 1.83 times higher in cells without cetuximab pretreatment. Fluorescence tracking with Cy5.5-labelled Cet-C8Pt(IV) further showed progressive cellular uptake over 6 h. Following internalisation, platinum release from Ab-Pt conjugates occur within endosomal or lysosomal compartments, typically triggered by acid-sensitive linkers or enzymatic cleavage. Successful release of the active platinum species is critical for cytosolic escape and subsequent nuclear targeting. Activated platinum species then form DNA adducts, disrupting replication and transcription. However, efficient endosomal escape remains a key factor influencing therapeutic efficacy, as entrapment in endosomes may limit access to nuclear DNA.

ADCs have demonstrated high efficacy by offering targeted delivery of cytotoxic drugs to tumours. However, they are limited by the payload they can carry. By integrating antibodies into drug-loaded nanocarriers, the ability of antibodies to deliver a wide range of therapeutic agents is significantly enhanced. Thus, platinum compounds were also encapsulated in carrier molecules bound to mAbs to further improve drug delivery and targeting (Fig. 5a). For instance, Ahn et al. developed an anti-tissue factor (TF) antibody fragment-antigen binding (Fab') conjugated to polymeric micelles containing an active complex of oxaliplatin, (1,2diaminocyclohexane)platinum(II) (DACHPt) (DACHPt/m, Fig. 5b) [77]. DACHPt/m was formed through maleimide-thiol conjugation and was designed to selectively deliver platinum drugs to pancreatic tumours. Notably, DACHPt/m demonstrated rapid cellular internalisation, resulting in enhanced in vitro cytotoxicity and effectively inhibiting the growth of pancreatic tumour xenografts in vivo, surpassing both non-targeted micelles and free drugs. Furthermore, Zalba et al. developed oxaliplatin (L-OH)-loaded liposomes linked to either whole cetuximab (CTX) or CTX-Fab' fragments to their surface (Fig. 5c, d) [78]. In EGFR-overexpressing cell lines, targeted liposomes achieved up to threefold higher intracellular drug delivery compared to non-targeted liposomes. When tested in a colorectal cancer (CRC) xenograft model, these ADCs significantly enhanced drug delivery, with CTX-Fab' L-OH-liposomes outperforming CTX-mAb L-OH-liposomes. This, in turn, was more effective than non-targeted liposomes and free drug treatment in mice with CRC. In addition, a novel ADC was synthesised incorporating ferritin-based nanoparticles where mAb Ep1 were conjugated to a single ferritin cage (Hft) encapsulating cisplatin [79]. Compared to cisplatin-containing ferritin nanoparticle alone, which were more effective in inhibiting thymidine incorporation in breast carcinoma than in melanoma cells, the HFt-Pt-Ep1 nanoparticle exhibited higher preference for melanoma cells. A similar preference for melanoma was observed in nude mice xenotransplanted with melanoma and breast carcinoma cells. This study identified the specific combinations and stoichiometric relationships between mAbs and nanoparticle protein cages, leading to the loss of tropism for ubiquitously distributed cellular receptors and the acquisition of

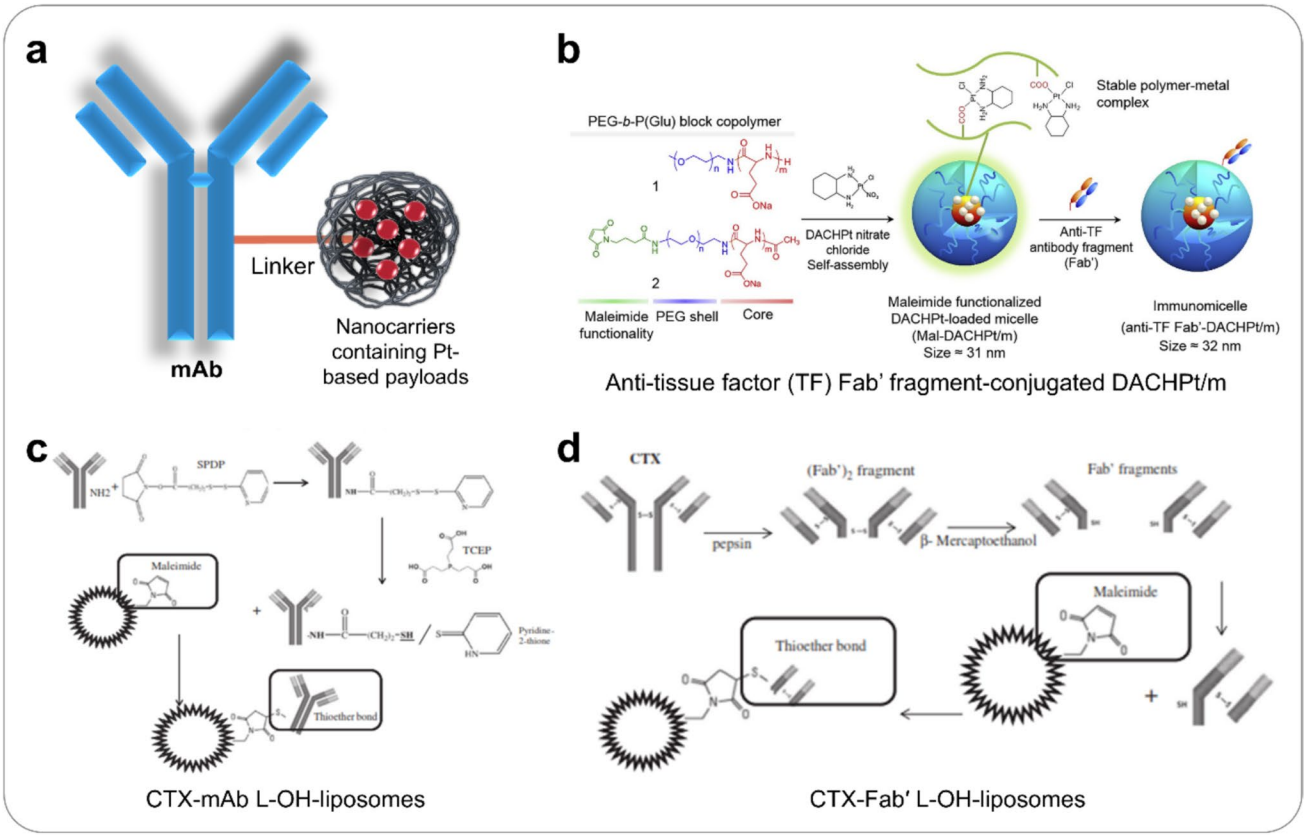


Fig. 5 Platinum-based ADCs as new strategies for specific tumour-targeting. **a** Platinum compounds are encapsulated in carrier molecules linked to mAbs to enhance drug delivery and targeting. **b** Schematic illustration of the preparation of an anti-tissue factor (TF) antibody fragment-antigen binding (Fab') conjugated to polymeric micelles containing an active complex of oxaliplatin, (1,2diamino-cyclohexane)platinum(II) (DACHPt) (DACHPt/m). Reprinted from [77], Copyright 2015, with permission from Elsevier. Schematic illustration of the method for preparing oxaliplatin (L-OH)-loaded liposomes linked to either (**c**) whole cetuximab (CTX) or (d) CTX-Fab' fragments to their surface. Reprinted from [78], Copyright 2015, with permission from Elsevier

lineage-selective binding. Moreover, another study developed oxaliplatin-loaded apoferritin conjugated with panitumumab via a polyethylene glycol (PEG) linker, which was designed to specifically target EGFR-overexpressing cell lines [80]. This ADC efficiently released oxaliplatin, inhibited tumour cell proliferation, and exhibited enhanced accumulation in tumour models with high EGFR expression in vivo. Remarkably, these studies have exhibited promising results, demonstrating that immune-nanocarriers can effectively enhance the therapeutic translational potential of ADCs containing platinum drugs. Due to the promising results obtained in these studies, ongoing efforts are currently underway to develop next-generation platinum-based ADCs.

Platinum resistance

Platinum-resistant cancer patients face limited and often ineffective treatment options, highlighting a significant unmet medical need. Moreover, the prognosis for these patients is generally poor, with lower survival rates compared to those with platinum-sensitive cancers [81]. Approximately 85% of ovarian cancer patients eventually develop resistance after an initial response to the treatment [82]. These patients typically have low response rates to further chemotherapy (< 15%), with a PFS of 3 to 4 months and a median survival of less than 1 year [81]. Mechanistically, cells can prevent cisplatin from reaching and harming DNA by reducing drug uptake, increasing drug efflux, and inactivating the drug through covalent binding to glutathione or metalloproteins [9, 10]. Additionally, resistance involves downstream responses such as altered apoptosis signalling and autophagy. If cisplatin does interact with DNA and cause damage, cells respond by enhancing repair mechanisms within the DNA damage response (DDR) pathways to counteract the effects. Therefore, identifying therapeutic strategies targeting DDR proteins involved in the repair of platinum-induced DNA lesions provides one approach to the development of potential strategies aimed to address platinum resistance and increase clinical benefit. This approach

is best illustrated by encompassing inhibitors of key mediators of DNA repair alongside platinum drugs in various recurrent cancers (NCT01237067 and NCT01033292) [83, 84]. Additionally, cyclin dependent kinases (CDKs) are also key regulators of DRR, which led to a phase I study examining the combination of ribociclib, a CDK4/6 inhibitor, with carboplatin/paclitaxel in patients with recurrent platinum-sensitive ovarian cancer (NCT03056833) [85]. Notably, this combination was deemed to be safe and feasible, with an ORR of 79.3% and the mPFS was 11.4 months. Moreover, histone deacetylase (HDAC) expression was significantly increased in resistant tumours [86]. Based on this, the non-kinase inhibitor of HDAC, quisinostat, was investigated in combination with carboplatin/paclitaxel in the clinic, particularly for recurrent cancer (NCT02948075 and NCT00772798) [87, 88]. Encouragingly, in patients with recurrent platinum-sensitive ovarian cancer, this combination showed significant responses and good tolerability (ORR: 62.2%, mPFS: 11.6 months; $P < 0.001$, and mOS: 40.6 months) [88]. Additionally, the mAb cetuximab in combination with platinum is an effective first-line regimen in recurrent/metastatic HNSCC patients, and subsequent studies examined the addition of patritumab, anti-HER3 mAb, to the cetuximab/platinum regimen (NCT02350712 and NCT02633800) [89, 90]. A phase Ib trial showed patritumab plus cetuximab/platinum was tolerable and active in recurrent and/or metastatic HNSCC [89]. The combination of iniparib with carboplatin and gemcitabine demonstrates notable clinical activity and is well tolerated in platinum-sensitive and -resistant recurrent ovarian cancer, particularly in patients with BRCA mutations (NCT01033123) [91]; however, given that iniparib is no longer considered a true PARPi and its mechanism of action remains unclear [92], the basis of this observed synergy warrants further investigation.

Effects of scheduling

Administration timing may be relevant in combination design, based on the notion that platinum-induced DNA damage and the activation of the DDR may need to occur first before the introduction of DNA repair inhibitors. This was shown by Li et al. in ovarian cancer models, where sequential administration of carboplatin and cell division cycle 7-related protein kinase (CDC7) inhibitor, XL413, showed synergistic enhancement of apoptosis [93]. Mechanistically, XL413 increases the accumulation of chemotherapy-induced DNA damage by inhibiting HR repair activity and delaying the recovery of DNA DSBs. This observation suggests that variable drug positioning, particularly delayed administration of DNA repair inhibitors following DNA-damaging agents, might increase treatment efficacy. For example, in a phase I/Ib trial, carboplatin was given before olaparib to patients with ovarian, breast, and uterine cancer [84]. Pharmacokinetic data from the trial suggested that administering carboplatin before olaparib may be the preferred treatment schedule to enhance the overall clinical benefit of this combination therapy, as pre-exposure to carboplatin causes intracellular accumulation of olaparib ($P = 0.013$), thereby improving its effective availability within tumour cells. These findings underscore the importance of exploring and optimising treatment scheduling to maximise their efficacy, particularly for future platinum drug combinations.

Combining platinum-based drugs with immunotherapy

The advent of frontline immunotherapy in clinical trials rapidly changed the treatment landscape, establishing it as the standard of care in some clinical situations [94]. Platinum-based drugs have demonstrated potential to induce an anti-cancer immune response by promoting the recruitment and activation of immune cells [95, 96], thereby enhancing the efficacy of immunotherapies. Thus, numerous efforts have been made to identify effective platinum/immunotherapy combinations, which have recently entered the clinical setting. This approach is particularly appealing to patients with advanced cancer, given their limited life expectancy and the drug-related toxicity associated with other combination chemotherapy regimens.

Immune checkpoint inhibitors (ICIs)

Immune checkpoint inhibitors (ICIs) such as anti-PD-1/PD-L1 and anti-CTLA-4 antibodies have obtained regulatory approvals across various tumour types and indications. ICIs work by activating the immune system of the body to identify and target cancer cells [97]. In 2011, based on promising results from a clinical trial in melanoma patients, the first ICI therapy ipilimumab, an anti-CTLA-4 mAb, has gained FDA approval [98]. Since then, ipilimumab was tested in numerous clinical trials for use in other cancer types. The subsequent triumphs in clinical trials paved the way for the approval of other anti-PD-1 mAbs, such as pembrolizumab, camrelizumab, sintilimab, toripalimab, and nivolumab, for treating a diverse range of malignancies [99]. Notably, the combination of pembrolizumab with platinum-based regimens has been evaluated in many cancers including NSCLC, SCLC, gastric, gastro-oesophageal junction, ovarian, urinary tract, endometrial, and BTC (NCT02549209, NCT02578680, NCT02580994, NCT02608684, NCT02853305, NCT02954536, NCT03029598, NCT03066778, NCT03664024, NCT03675737, NCT03582475, and NCT04003636) [100–111]. In the phase III KEYNOTE-189 trial of previously untreated metastatic

NSCLC patients, the addition of pembrolizumab to platinum/pemetrexed chemotherapy improved efficacy outcomes with manageable toxicity [100]. Amongst 57 patients who completed 35 cycles of pembrolizumab/chemotherapy, the ORR was 86.0% and the 3-year OS rate was 71.9%. The benefit of pembrolizumab correlated with PD-L1 expression levels, with greater efficacy in patients with a tumour proportion score (TPS) ≥ 50%. In the intent-to-treat (ITT) population, the 5-year OS rate was approximately 20% with pembrolizumab plus chemotherapy compared to 11% with placebo plus chemotherapy, with higher survival observed in patients with TPS ≥ 50% (29.6% v 21.4%). Notably, in patients with advanced endometrial cancer, the addition of pembrolizumab to carboplatin/paclitaxel was found to improve ORR and was well tolerated compared to the placebo/chemotherapy group (ORR: 74.4%; $P = 0.001$, and mPFS: 10.6 months) [108]. In addition, results from phase III trials in advanced BTC patients showed that the addition of pembrolizumab to cisplatin/gemcitabine revealed an improvement in OS compared to cisplatin/gemcitabine alone without any new safety signals (mOS: 12·7 vs. 10·9 months; one-sided $P = 0.0034$ [significance threshold $P = 0.02$]) [110]. Additionally, in the KEYNOTE-859 phase III trial assessing patients with locally advanced or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma, adding pembrolizumab to platinum/chemotherapy treatment significantly improved OS with a manageable toxicity profile compared to the placebo/chemotherapy group [111]. As such, these studies support the concept of adding pembrolizumab to platinum-based regimens as first-line treatment for various metastatic/advanced cancers. Despite the positive clinical responses observed, several studies demonstrated that these combinations did not significantly improve efficacy or provide benefit beyond chemotherapy alone in patients with untreated extensive-stage SCLC [101], recurrent platinum-resistant ovarian cancer patients [105], or advanced urothelial carcinoma patients [106]. This treatment also did not improve the durability of response in patients with platinum-resistant recurrent ovarian cancer compared to platinum chemotherapy alone, although the combination regimen was well tolerated with no discontinuations due to treatments-related toxicity [105].

In the CANTABRICO phase III trial, anti-PD-L1 durvalumab, was examined in combination with platinum/etoposide regimen in extensive-stage SCLC patients (NCT04712903 and EudraCT 2020–002328-35) [112]. This study demonstrated good clinical benefits with favourable safety profile (ORR: 51.5%; mPFS: 6.1 months and 6-month PFS rate: 50.2%). In another phase III trial, durvalumab with cisplatin/gemcitabine significantly showed improvements compared to the placebo/chemotherapy group in patients with BTC (24-month OS rate: 24.9% vs. 10.4% and ORR: 26.7% vs. 18.7%; NCT03875235) [113]. In another intriguing approach, anti-CTLA-4 mAb, ipilimumab, was added to nivolumab/platinum-doublet chemotherapy regimens where this combination was found effective and tolerable as a first-line treatment of advanced/metastatic NSCLC (NCT02659059) [114]. Another anti-CTLA-4 mAb, tremelimumab, was added to durvalumab/cisplatin/5-FU treatment where manageable safety and anti-tumour activity in patients with advanced or metastatic ESCC were shown (OR: 37.5%; mPFS: 3.75 months and mOS: 9.69 months; NCT02658214) [115], warranting further investigation in randomised trials.

Sintilimab was also examined in combination with a platinum-based regimen in patients with advanced or metastatic NSCLC (NCT02937116 and NCT03629925) [116, 117]. In these patients, this combination showed good clinical efficacy (ORR: 68.4%, and mPFS: 11.4 months), with an acceptable safety profile [116]. Other trials also examined toripalimab (NCT04144608) [118], and nivolumab (NCT02944396) [119], in combination with platinum-based regimens in NSCLC patients. Promisingly, the addition of toripalimab to a platinum-based regimen demonstrated robust anti-tumour activity with good tolerability in patients with potentially resectable NSCLC [118]. Of note, the combination of cemiplimab-rwlc, mAb targeting PD-1, in combination with platinum-based chemotherapy has gained FDA approval as first-line treatment for adult patients with advanced NSCLC [120].

Oncolytic viruses, cytokines, and cancer vaccines

Other alternative immunotherapeutic approaches include oncolytic viruses, cytokines, and cancer vaccines, which represent potent approaches for treating certain aggressive and refractory cancers. For example, pelareorep (REOLYSIN), is an investigational novel oncolytic virus composed of a live, replication-competent, Reovirus Type 3 Dearing strain in a proprietary formulation [121]. Preclinical data demonstrated that pelareorep induces antineoplastic activity across various cancers types, particularly in cells with an activated RAS-signalling pathway [122]. In a randomised phase II trial, the combination of pelareorep with carboplatin/paclitaxel was safe but did not improve PFS in patients with metastatic pancreatic adenocarcinoma (NCT01280058) [123]. However, in another study, the addition of pelareorep to the carboplatin/paclitaxel regimen was both safe and showed promising clinical activity in patients with advanced malignant melanoma, with a mPFS of 5.2 months, mOS of 10.9 months and 1-year OS rate of 43% (NCT00984464) [124], warranting further randomised phase III trials. The tumour necrosis factor (TNF) is a pivotal proinflammatory cytokine that influences various aspects of the immune response [125]. The safety, efficacy, and pharmacodynamic effects of the addition of certolizumab, a TNF inhibitor, to cisplatin/pemetrexed regimen was evaluated in stage IV lung

adenocarcinoma patients (NCT02120807) [126]. This treatment modality was well tolerated and the mPFS was 7.1 months.

In addition to cytokines, cancer vaccines are emerging as promising immunotherapies, demonstrating a level of therapeutic efficacy that surpasses or equals that of other treatments in certain contexts, which is considered high relative to current standards of care [127]. For example, dendritic cell vaccination is a safe immunotherapeutic approach that works by harnessing the body's own immune system. It involves isolating dendritic cells from a patient, loading them with tumour antigens, and then reinfusing them into the patient to elicit both immunological and clinical responses in solid tumour patients. These antigen-presenting cells stimulate T cells to recognise and attack tumour cells, thereby potentially reducing tumour growth and improving patient outcomes. In a phase I/II study, the addition of dendritic cell vaccination to a carboplatin/paclitaxel regimen was safe and tolerable in patients with metastatic endometrial cancer (NCT04212377) [128]. Subsequently, the dendritic cell-based immunotherapy, DCVAC/OvCa, was combined with carboplatin/gemcitabine regimen in a phase II trial to evaluate their safety and efficacy in platinum-sensitive ovarian cancer (NCT02107950) [129]. DCVAC/OvCa combined with chemotherapy significantly prolonged mOS compared to the placebo/chemotherapy group (35.5 vs. 22.1 months; $P = 0.003$), and had a favourable safety profile. Moreover, the field of oncolytic virotherapy is progressing, as evidenced by a phase III clinical trial investigating the investigational oncolytic virus olvimulogene nanivacirepvec (Olvi-Vec) administered in combination with platinum-doublet chemotherapy and bevacizumab for the treatment of platinum-resistant or refractory ovarian cancer (NCT05281471) [130]. This trial highlights the ongoing efforts to combine virotherapy with traditional chemotherapy and immunotherapy modalities in cancer treatment.

Comparative effectiveness of platinum-based combination strategies in different malignancies

Although platinum combinations are widely used in multiple malignancies, clinical outcomes vary significantly depending on cancer type and partner drugs. In advanced NSCLC, platinum combinations with immune checkpoint inhibitors or anti-angiogenic therapies have demonstrated improved clinical outcomes. For example, pembrolizumab combined with cisplatin and pemetrexed showed an ORR of 86% and a 3-year OS of 71.9% in previously untreated metastatic non-squamous NSCLC (NCT02578680), illustrating the potential of immunotherapy-platinum combinations [100]. In extensive-stage SCLC, platinum-etoposide remains a standard regimen, with immune checkpoint inhibitors further improving outcomes. Pembrolizumab combined with platinum-etoposide demonstrated an ORR of 70.6% and a 12-month PFS of 13.6%, whilst durvalumab showed an ORR of 51.5% and mPFS of 6.1 months (NCT03066778 and NCT04712903) [103, 112].

In ovarian cancer, carboplatin-based doublets remain the cornerstone of therapy, with paclitaxel-carboplatin showing robust survival outcomes across multiple phase III trials (mPFS 16.8–20.7 months, mOS up to 57.4 months; NCT00326456) [131]. Substituting paclitaxel with PLD has yielded even longer survival (mPFS 19.0 months, mOS 61.6 months), especially in partially platinum-sensitive patients. Early-phase trials incorporating agents like veliparib or gemcitabine have demonstrated response rates up to 45%, and mirvetuximab soravtansine has shown an ORR of 71% and mPFS of 15 months (NCT02606305) [73]. In HNSCC, platinum-based regimens combined with cetuximab remain a standard treatment, with the EXTREME regimen achieving mOS of 10.1 months and PFS of 5.6 months (NCT00122460) [132]. The TPEx regimen further improved mOS to 14.5 months (NCT02268695) [63]. Encouragingly, combinations with veliparib or HER-targeting agents like panitumumab and patritumab demonstrated mOS up to 13.5 months (NCT00454779, NCT02633800) [90, 133].

In TNBC, platinum-based combinations have been linked to improved pCR rates, particularly in early-stage disease. For instance, neoadjuvant paclitaxel plus carboplatin achieved a pCR of 52% and a 36-month EFS of 79% in the PARTNER trial (NCT03150576) [58, 59]. Adding olaparib yielded a pCR of 51% and slightly improved 36-month EFS (80%) and overall survival (90%). Other regimens, such as carboplatin with docetaxel or with cyclophosphamide and doxorubicin, showed pCR rates between 52 and 55% (NCT02413320) [27]. In the metastatic setting, platinum-PARPi combinations have demonstrated promising activity in TNBC, including those without BRCA mutations. For example, veliparib with carboplatin and paclitaxel resulted in a mPFS of 16.6 months in TNBC patients (NCT02163694) [57]. Finally, in BTC, cisplatin-gemcitabine remains the standard first-line therapy, with mOS ranging from 12.6 to 13.5 months and mPFS of 5.5–7.4 months (NCT02182778) [30]. Enhancing this regimen with nab-paclitaxel has resulted in mOS improvements up to 19.2 months and high disease control rates (84%) (NCT02392637) [33]. In contrast, carboplatin-paclitaxel remains the backbone of first-line therapy in ovarian cancer, with phase III trials showing mOS up to 44.8 months and mPFS of 16.2 months (NCT00028743) [134].

Other therapeutic strategies for platinum-based drugs

Combining platinum-based drugs with stem cell therapies

Besides the described treatment modalities, stem cell therapies, including stem cell transplants, in combination with platinum regimens, represent a promising approach for treating certain aggressive and refractory cancers. These have been the focus of phase III clinical trials in patients with relapsed hodgkin's lymphoma (NCT00025636) [135, 136], and men with previously untreated germ cell cancer (NCT00003941) [137]. Notably, in patients with relapsed or refractory germ cell tumours, the inclusion of stem cell transplants in the cisplatin/cytotoxic regimen demonstrated clinical benefits, with a 2-year PFS rate of 67% and a 2-year OS rate of 72% (NCT02375204) [138], indicating potential for regulatory approval and broader clinical application, albeit with the need for careful patient selection and management due to associated risks and side effects.

Dual-drug codelivery nanosystems

Since the approval of nanotherapeutics that are commercially available, such as Abraxane® (nab-paclitaxel), Doxil® (liposomal doxorubicin), Onivyde® (liposomal irinotecan), and Vyxeos® (daunorubicin and cytarabine liposome), there has been a growing interest in nanocarrier approaches to deliver therapeutic agents. Nanocarriers offer several advantages, including enhancing the water solubility of poorly soluble drugs, prolonging their circulation time in the blood, and facilitating drug targeting to tumours [139]. This targeted delivery increases drug availability within tumour cells whilst mitigating the toxic and off-target side effects typically associated with traditional chemotherapy. The benefits of encapsulating platinum drugs in nanoparticles to reduce side effects without compromising efficacy have been demonstrated in tumour-bearing mice and preclinical cancer models [140]. Also, the tumour-localised drug delivery strategies exhibit benefits for preventing local tumour recurrence [141]. Several nanocarriers for cisplatin have entered clinical trials. For example, Lipoplatin, a liposomal cisplatin formulation, which has reached phase III trials and demonstrated excellent encouraging anti-cancer efficacy in several tumour types, including lung, colon, gastric, and prostate cancers [142], although clinical adoption remains limited. Another formulation, NC-6004, is a poly(glutamic acid) (PGlu)-based polymeric micelle containing cisplatin. In early-phase trials involving patients with advanced solid tumours, NC-6004 demonstrated reduced nephrotoxicity compared to cisplatin alone [143]. It has been further investigated in clinical studies in combination with gemcitabine [144–146] and pembrolizumab [147]. Despite mixed clinical outcomes, these formulations highlight the ongoing efforts and challenges in optimising nanocarrier-based platinum drug delivery systems. In preclinical studies, various nanocarriers have also been utilised for dual-drug codelivery of cisplatin/paclitaxel including telodendrimers [148], polymeric micelles [149], and nanostructured lipid carriers [150, 151] as well as cisplatin/doxorubicin combinations using hyaluronic acid micelles [152], and mesoporous silica NPs (MSNs) [153]. These studies demonstrated that dual-drug nanocarriers enhance pharmacokinetics by improving solubility, protecting drugs from rapid degradation, enabling extended release, bypassing first-pass metabolism, and providing targeted delivery.

Multi-targeted platinum compounds

In contrast to the serendipitous discovery of the first-in-class drug, cisplatin, the subsequent development of platinum metallodrugs has relied heavily on rational drug design. A thorough analysis of the mechanism of action and adverse effects linked with the first-generation drug has enabled the rectification of these issues in the development of subsequent agents. Amidst the evolving landscape of reformed and newly developed platinum drugs, multi-targeted platinum compounds have garnered considerable attention for their potential in cancer-specific therapy [154]. This focus has spurred extensive research into leveraging cellular targets beyond DNA for therapeutic interventions involving platinum compounds. For example, Fronik et al. developed a triple-action platinum(IV) prodrug, designed for tumour targeting via maleimide-mediated albumin binding, also for release of the immunomodulatory ligand 1-methyl-d-tryptophan (1-MDT) [155]. Structure–activity relationship analysis unexpectedly revealed that the mode of 1-MDT conjugation significantly influences the prodrug's reducibility and activation. This, in turn, affects ligand release, pharmacokinetics, immunomodulatory efficiency, and anticancer activity both in vitro and in vivo. The use of albumin-targeted, multi-functional platinum(IV) prodrugs represents a promising strategy to enhance the intracellular delivery of low-permeability bioactive ligands like 1-MDT and to improve their selective accumulation in tumours, thereby enabling tumour-specific therapy supported by a modulated immune microenvironment.

Enzymes, integral to nearly all physiological and pathophysiological processes, have long been recognised as promising drug targets. Several studies have thus developed

dual-functioning platinum complexes, incorporating a HDAC inhibitor (HDACi) within the platinum framework. For instance, *cis*-[$Pt^{II}(NH_3)_2$(malSAHA $-_{2H}$)] (Pt-malSAHA) comprising both a cisplatin core and the HDACi, SAHA, has demonstrated DNA binding properties and HDAC inhibitory activity (Fig. 6) [156]. Remarkably, Pt-malSAHA exhibited potent cytotoxicity across various cancer cell lines, including ovarian, colon, lung, and breast cancer cells, with notably enhanced cancer selectivity over normal cells. Subsequently, Belinostat, a second-generation analogue of SAHA was combined within a platinum(II) framework, to develop *cis*-[$Pt^{II}(NH_3)_2$(mal-*p*-Bel $-_{2H}$)] (Pt-malBel) (Fig. 6) [157], showing similar cytotoxicity to Pt-malSAHA in A2780 ovarian cells and significant potency against cisplatin-resistant A2780cisR ovarian cancer cells. Additionally, two novel trans-platinum(II) complexes incorporating the HDACi valproic acid (VPA), named *trans*-[Pt(VPA $-_{1H})_2(NH_3)$(py)] and *trans*-[Pt(VPA $-_{1H})_2(py)_2$], where py is pyridine were developed [158]. These complexes showed only marginally enhanced cytotoxicity against A2780 and A2780cisR cells compared to cisplatin.

In addition to HDACi, new complexes combining a CDK inhibitor, bohemine or its derivatives, within a platinum(II) framework were developed, namely, *cis*-[Pt(2-(3-hydroxypropylamino)6-benzylamino-9-isopropylpurine)$_2Cl_2$], *cis*-[Pt(2-chloro-6-benzylamino-9-isopropylpurine)$_2Cl_2$], and *cis*-[Pt(2-chloro-6-[(4methoxybenzyl)amino]−9-isopropylpurine)$_2Cl_2$] (Fig. 6), demonstrating cytotoxicity comparable to or greater than that of cisplatin against ovarian cells [159]. Interestingly,

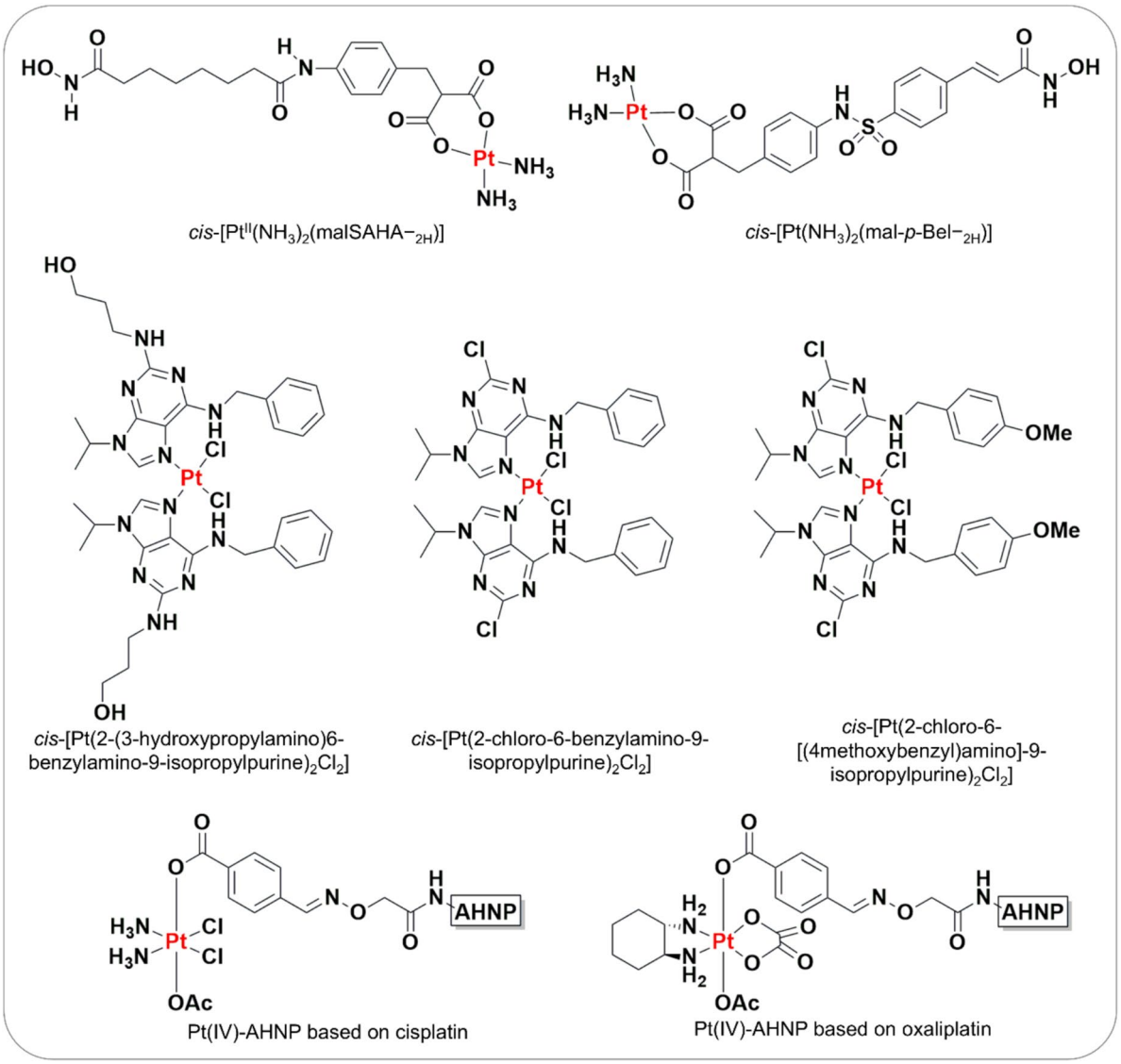


Fig. 6 Structures of investigational multi-targeted platinum compounds

the increased cytotoxicity was not attributed to CDK inhibitory activity, as CDK inhibition was lost when bohemine was complexed with the platinum(II) core. However, the complexes induced significant DNA platination, suggesting DNA binding as their primary mechanism of action. In another study, Wong et al. developed platinum(IV)-peptide conjugates using a cisplatin or oxaliplatin core, incorporating an anti-HER2/neu peptide (NH2-Tyr-Cys-Asp-Gly-Phe-Tyr-Ala-Cys-Tyr-Met-Asp-Val-Gly-Gly-Lys-Lys(aminooxy)-CONH2, or ANHP) (Fig. 6) [160]. These complexes demonstrated cytotoxicity comparable to cisplatin and oxaliplatin, and showed selective targeting for HER2-overexpressing NCI-N87 gastric cancer cells and BT-474 breast ductal carcinoma cells, both of which are resistant to apoptosis. Importantly, these platinum complexes exhibited enhanced selectivity for cancerous cells over normal cells, with their accumulation in HER2 cancer cells facilitated by the HER2-targeting peptide ligand. Overall, these innovative approaches to drug design have yielded new families of platinum metallodrugs, potentially mitigating the systemic toxicities associated with contemporary chemotherapeutics and addressing resistance issues.

Conclusion and future perspectives

In conclusion, platinum-based combinations with various drug classes have shown promising clinical responses in randomised studies across various cancer types, surpassing the efficacy of traditional single-drug regimens. However, the limitations of established platinum/cytotoxic combinations, such as toxicity and drug resistance issues, highlight the necessity for innovative approaches. Newer platinum combinations, such as those with targeted therapies and immunotherapies, have demonstrate improved tolerability. Notably, combining platinum drugs with DDR inhibitors shows promise in targeting resistant cancers, and pairing platinum drugs with emerging treatment modalities likes oncolytic viruses, cancer vaccines, and cytokines holds significant potential. Whilst the potential benefits are substantial, these studies highlight the need to select platinum combinations for investigation in appropriate disease settings and patient populations to attain clinical benefit. As such, ongoing research efforts are focussed on optimising treatment regimens and identifying predictive biomarkers of therapy response to refine patient selection and maximise clinical benefits. Advances in molecular profiling and personalised medicine are likely to lead to more precise targeting of cancer cells, reducing the risk of toxicity and increasing the efficacy of treatment.

Whilst platinum-based ADCs and multi-targeted platinum compounds have not yet entered clinical trials, promising preclinical data suggest their potential clinical application. With extensive ongoing efforts to develop next-generation platinum compounds by identifying new targets and enhancing their pharmacological properties, it is likely that multi-targeted platinum drugs will reach the clinical stage in the near future. Additionally, advancements in drug delivery systems could improve the bioavailability and selectivity of platinum compounds through dual-drug delivery strategies, further enhancing their therapeutic potential [161]. Another promising avenue for future research is the integration of artificial intelligence (AI) in drug discovery and precision oncology. AI and machine learning models can facilitate the identification of optimal platinum-based combinations, predict patient responses using multi-omics data, and refine clinical trial designs, accelerating the development of more effective therapies [162]. Looking ahead, platinum-based combination therapies are poised to play a pivotal role in cancer management, offering more effective and less toxic treatment options. By leveraging emerging technologies, refining patient stratification, and advancing drug formulations, platinum-based chemotherapy is set to drive significant progress in oncology treatment.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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