PD-1 blockade synergizes with oxaliplatin-based, but not cisplatin-based, chemotherapy of gastric cancer

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ABSTRACT
Preclinical experimentation revealed that established cancers treated with the immunogenic cell death (ICD) inducer oxaliplatin are sensitized to immune checkpoint inhibitors targeting PD-1. In contrast, no such sensitizing effect is observed when cisplatin, a non-immunogenic cell death inducer is used. Two randomized phase III clinical trials targeting unresectable gastric and gastro-esophageal junction carcinomas apparently validate this observation. Thus, oxaliplatin-based chemotherapy (together with capcitabine or 5-fluorouracil plus leucovorin) favorably interacted with nivolumab, yielding improved outcome. In contrast, the outcome of cisplatin-based chemotherapy (together with capcitabine or 5-fluorouracil) failed to be improved by concomitant treatment with pembrolizumab. These clinical findings underscore the importance of choosing appropriate ICD-inducing cytotoxicants for the development of chemoinmunotherapeutic regimens. Unfortunately, the FDA and EMA have approved PD-1 blockade in combination with “platinum-based chemotherapy” without specifying the precise nature of the platinum-containing drug. This is a non sequitur. Based on the available clinical data, such approvals should be restricted to the use of oxaliplatin.

Main text
Platinum-based antineoplastic drugs are among the most widely used chemotherapeutic agents employed for the treatment of solid tumors including but not limited to lung, colorectal, gastric, and head and neck cancers. Cisplatin is a first-generation platinum drug initially approved by the FDA for testicular and ovarian cancers and has been, and still is, one of the most employed chemotherapeutic agents in clinical routine. Despite the landmark success during the dawn of chemotherapy in the 1970s, major limitations of cisplatin are the (inevitable) occurrence of drug resistance as well as considerable side effects. Since then, new generation analogues with equivalent or increased antitumor activity and decreased risk of adverse effects have been developed and introduced into clinical oncology. Oxaliplatin, a second generation anticancer agent, turned out to be as efficient as cisplatin in the treatment of gastric cancers. Systematic meta-analysis of clinical trials in advanced gastric cancer comparing oxaliplatin-based treatment regimens with cisplatin-mediated effects revealed equivalent or superior antineoplastic effects of oxaliplatin that were coupled to a favorable safety profile associated with less neuropenia and fewer thromboembolic events, but with increased neurotoxicity. Of note, accumulating evidence suggests that the improved anticancer efficacy of oxaliplatin depends at least in part on the induction of immunogenic cell death (ICD), which stimulates potent antitumor immune responses.

ICD is a functionally unique form of regulated cell death that is accompanied by the exposure and release of damage-associated molecular patterns (DAMPs), which are recognized by pattern recognition receptors (PRRs) expressed on antigen presenting cells (APC) such as dendritic cells (DCs). ICD-associated DAMPs include ATP and annexin A1 (ANXA1), the secretion of which enable the recruitment and chemotaxis of DCs; the surface exposure of calreticulin (CALR) that serves as an “eat-me” signal facilitating the phagocytosis of dying cells by DCs; and the release of nuclear DNA-binding protein high mobility group box 1 (HMGB1) by the tumor that promotes DC maturation and stimulates tumor antigen cross-presentation. Moreover, type 1 IFN secreted by the tumor in the context of ICD triggers autocrine and paracrine circuitries that result in the release of chemokine (C-X-C motif) ligand 10 (CXCL10), which mediates chemotactic and immunostimulatory effects. Altogether, the ICD-associated emission of DAMPs confers robust adjuvanticity, which in turn stimulates tumor antigen-specific immune responses and the generation of long-term immunological memory. Such immunological consequences are not strictly
linked to the chemical structure of the employed chemotherapeutic agent. Thus, tumor cells undergoing ICD in response to oxaliplatin have the ability to trigger protective immune responses when injected into immunocompetent animals without any adjuvants, whereas cells succumbing in response to cisplatin fail to induce such a vaccinating effect, providing an explanation for the observation that cisplatin is less efficient in controlling cancer than oxaliplatin in several preclinical models.\textsuperscript{11,24} 

In the past decade immune checkpoint inhibitors (ICIs), such as monoclonal antibodies targeting programmed cell death protein 1 (PD-1) (PD-1), have become a frontline therapy for many types of cancer, including those with a high mutational burden and mismatch repair deficiency.\textsuperscript{25} However, in many cases ICI monotherapy fails to confer sufficient benefit due to the lack of pre-existing immune priming.\textsuperscript{26–28} Therefore, ICD-inducing regimens that are capable of stimulating adaptive antitumor immunity appear as particularly promising combinations for generating synergistic effects with ICIs. The concept of combining immunogenic chemotherapies with ICIs is supported by several preclinical studies generally employing ICD inducers to prime an adaptive antitumor immune response several days or weeks before the administration of ICIs (Table 1).\textsuperscript{31,54} Considerable research efforts have been dedicated to combination therapies consisting of oxaliplatin-based immunogenic chemotherapies and PD-1/PD-L1 blocking antibodies in orthotopic models of fibrosarcoma,\textsuperscript{31,24,29,32} lung,\textsuperscript{33–37} colon,\textsuperscript{55} liver\textsuperscript{55} and gastric cancer.\textsuperscript{38} Importantly, these preclinical studies not only described synergistic interactions between oxaliplatin and PD-1/PD-L1 blockade, but also unraveled the role of ICD in reshaping the tumor microenvironment. Pfirschkoe and colleagues employed oxaliplatin together with cyclophosphamide on a Kirsten rat sarcoma viral oncogene homolog (KRAS) mutated and tumor suppressor p53 (TP53) deficient (KP) non-small cell lung cancer (NSCLC) model. This model exhibits an extremely poor infiltration by CD3\textsuperscript{+} T cells at baseline and thus resists all current monotherapy options including PD-1 blocking antibodies.\textsuperscript{29} This study revealed that oxaliplatin plus cyclophosphamide induced potent ICD in the KP model, accompanied by a significant infiltration of tumor nodules by CD3\textsuperscript{+} T cells, as well as a rise of CD8\textsuperscript{+} cytotoxic T lymphocytes (CTL) over regulatory T cells (Tregs). Altogether, the treatment with oxaliplatin reestablished cancer immunsurveillance and hence sensitized KP lung cancers to subsequent immunotherapy with PD-1 and CTLA-4 blockade.\textsuperscript{29} This finding has been confirmed in additional lung cancer models,\textsuperscript{34,33,38} as well as other cancer types,\textsuperscript{30,34,38} which all exhibited increased tumor infiltrating T cells and synergistic effects of oxaliplatin with PD-1/PD-L1 ICI. Interestingly, Shivani et al. demonstrated the recruitment of CAR-T cells into murine lung cancers treated with oxaliplatin,\textsuperscript{56} thus sensitizing those treatment-resistant tumors to anti-PD-L1, which makes oxaliplatin an attractive companion treatment for adoptive T cell transfer, particularly when combined with T cell-targeting ICIs. Moreover, in addition to CTLs, other immune cells, such as nature killer (NK)\textsuperscript{24,57} and dendritic cells (DC)\textsuperscript{35} can be recruited into tumors that are treated with oxaliplatin, underscoring the immunostimulatory effect of the agent. 

Apart from enriching the tumor infiltrate with immune effectors, oxaliplatin also depletes immunosuppressive cells, including tumor-associated macrophages (TAM) and myeloid-derived suppressive cells (MDSC),\textsuperscript{38,58} thus favorable remodeling the tumor microenvironment. The expression level of PD-L1 in cancer cells is an important prognostic parameter to predict the efficacy of PD-1/PD-L1 blockade. Interestingly, a direct consequence of the induction of ICD by oxaliplatin is the upregulation of PD-L1 expression in many types of cancer and myeloid cells.\textsuperscript{32,33,38} This provides yet another rationale for the combination of oxaliplatin with PD-1/PD-L1 ICIs. Of note, oxaliplatin-mediated synergistic effects with ICIs may also link to its capacity to induce systemic antitumor immune responses, which occur in both preclinical mouse models\textsuperscript{59} and high-risk rectal cancer patients.\textsuperscript{60} Taken together, these studies underline the notion that ICD induction with oxaliplatin alters the tumor immune microenvironment, converting ‘cold’ into ‘hot’ tumors, while in parallel affecting systemic immune regulation, eventually resulting in the sensitization to subsequent ICI immunotherapies (Figure 1). Several clinical trials recently confirmed that the pretreatment with ICD-inducing oxaliplatin sensitizes to immunotherapy with ICIs targeting the PD-1/PD-L1 pathway and yields an improved control of advanced gastric carcinomas, known for their particularly poor prognosis. A Phase I b trial in patients with advanced gastric or esophagogastric junction cancer confirmed the tolerability and efficacy of oxaliplatin-based chemotherapy in combination with PD-1 blocking antibodies employed as a first-line treatment.\textsuperscript{61} Moreover, systematic reviews of gene expression profiles in patient biopsies revealed the importance of immune infiltration as an indicator for patient prognosis and a predictive factor for immunotherapy in gastric cancers.\textsuperscript{62,63} Consistent with the aforementioned preclinical studies, the positive effects of oxaliplatin-based immunogenic (neoadjuvant) chemotherapy on the immune microenvironment has been confirmed by the meta-analysis of in silico data, as well as by multiplex immunostaining and next-generation sequencing (NGS) of gastric cancer biopsies,\textsuperscript{64} altogether showing an elevated level of CTLs in the tumor immune infiltrate of patients treated with oxaliplatin, correlating with improved objective response rates. More direct proof for the synergistic effect of oxaliplatin and ICI therapy comes from the recent clinical trial CheckMate 649\textsuperscript{65} targeting unresectable gastric and gastro-esophageal junction carcinomas. This trial apparently validates the observation that oxaliplatin exerts beneficial synergistic effects with PD-1 blockade, while in another comparable study (Keynote 062,\textsuperscript{66}) the non-ICD inducing platinum agent cisplatin failed to do so. As shown in Table 2, the studied arms in each trial were well balanced for all prognostic factors, which were comparable among these two trials. In the CheckMate 649 trial, the combination of oxaliplatin-based chemotherapy with PD-1 blockade led to a significant improvement of overall survival (OS) and progression-free survival (PFS) as compared to chemotherapy alone. In contrast, the improvement of survival was much less profound when PD-1 blockade was added to cisplatin-
based chemotherapy in the KEYNOTE-062 study. Specifically, the median OS of patients (PD-L1 CPS ≥ 1) in the chemotherapy alone group was equivalent in the KEYNOTE-062 and CheckMate 649 studies (11.1 and 11.3 months, respectively). However, substantial benefits from additional combination of PD-1 blockade was exclusively found in the CheckMate 649 study in which oxaliplatin (median OS: 11.3 vs 14.0 months without vs with Nivolumab, HR = 0.77, P < 0.0001) was used rather than cisplatin as in KEYNOTE-062 (median OS: 11.1 vs 12.5 months without vs with Pembrolizumab, HR = 0.85, P = 0.05). Notably, the objective response rate (ORR) of patients in both arms was numerically higher in the CheckMate 649 study compared with that in the KEYNOTE-062, indicating that oxaliplatin is associated with greater response in gastric cancer either with or without PD-1 blocker. These results suggest that oxaliplatin-based chemotherapy is more likely to synergize with PD-1 antibody in the treatment of HER-2 negative gastric cancers, leading to greater survival benefits as compared to cisplatin.

Intriguingly, another trial, Keynote-811, evaluated the benefit of combining pembrolizumab (PD-1 blocking monoclonal antibody) with chemotherapy (investigators’ choice) plus trastuzumab (HER2 blocking monoclonal antibody) in the treatment of HER-2 positive gastric or GEJ adenocarcinoma. Researchers found that adding PD-1 blockade to trastuzumab and chemotherapy led to a significant 22.7% improvement (from 51.9% to 74.4% without vs with PD-1 blockade, P = 0.00006) in ORR. It should be noted that the majority of patients (>86%) in this study received oxaliplatin-based chemotherapy as compared to 100% of cisplatin in the KEYNOTE-062 study.
Table 1. Preclinical studies combining ICD inducers and PD-1/PD-L1 blockade.

| ICD inducer                        | PD-1 / PD-L1 | Cancer models               | Treatment procedure | Observations                                                                 | Ref |
|------------------------------------|--------------|----------------------------|---------------------|-------------------------------------------------------------------------------|-----|
| Oxaliplatin + cyclophosphamide     | PD-1 + CTLA-4| KRAS and TRP53 (KP) mutant lung cancer | Sequential          | Restores the sensitivity of a multi treatment-resistant lung cancer model to PD-1 and CTLA-4 blockade | 29  |
| Oxaliplatin + cyclophosphamide     | PD-L1        | KRAS and TRP53 (KP) mutant lung cancer | Sequential          | Enhances recruitment of CAR-T cells to lung tumors and sensitizes tumors to PD-L1 blockade | 30  |
| Oxaliplatin or mitoxantrone        | PD-1 + CTLA-4| Fibrosarcoma                | Sequential          | Oxaliplatin combination with CRMs synergize with ICI                                                                 | 31  |
| Oxaliplatin                        | PD-L1        | LLC                        | Simultaneous        | Oxaliplatin treatment led to increased PD-L1 expression on LLC cells and synergize anti-PD-L1 | 32  |
| Oxaliplatin                        | PD-1         | LLC                        | Simultaneous        | Oxaliplatin treatment improves tumor infiltration of T and NK cells and synergize with different ICI | 33  |
| Oxaliplatin                        | PD-1         | Hepatocellular carcinoma   | Sequential          | Combination therapy of oxaliplatin and pd-1 exert better anticancer effect than monotherapy | 34  |
| Oxaliplatin + pemetrexed           | PD-1         | Colorectal cancer          | Simultaneous        | Oxaliplatin boosts anti-PD-L1 effect in an orthotopic colorectal tumor model | 35  |
| Oxaliplatin + pemetrexed           | PD-1         | Colorectal cancer          | Simultaneous        | Oxaliplatin + pemetrexed increase DC and T cell infiltration, potentiate pd0-1 for regressing murine colorectal cancer | 36  |
| Oxaliplatin + trifluoridine/tipiracil | PD-1     | Colorectal cancer          | Simultaneous        | Oxaliplatin + FTD/Tpi induce ICD in vivo and potentiate pd0-1 effect | 37  |
| Oxaliplatin + capecitabine          | PD-L1        | Colorectal cancer          | Simultaneous        | Oxaliplatin + capecitabine potentiate pd0-L1 effects | 38  |
| Oxaliplatin + S-FU                  | PD-1         | Gastric cancer             | Simultaneous        | Oxaliplatin + S-FU increase cytotoxic T cell infiltration, deplete MDSCs in gastric tumors and increased the response to pd-1 | 39  |
| PT-112 (a platinum-pyrophosphate conjugate) | PD-1 | Colorectal cancer | Sequential          | PT-112 synergizes with PD-1 or PD-L1 blockade to eradicate established mouse colon tumors | 40  |
| Lorberincedtin                      | PD-1         | NSCLC; Fibrosarcoma        | Sequential          | Crizotinib-induced ICD sensitizes pd0-L1 in implantable, carcinogen- or oncogene induced orthotopic NSCLC models | 41  |
| Crizotinib in combination with cisplatin | PD-1       | NSCLC; Fibrosarcoma        | Sequential          | Crizotinib and cetinib induce ICD and synergize with pd0-L1 in ALK-dependent ALCL | 42  |
| Cetinib                             | PD-1         | ALCL                       | Sequential          | Crizotinib-induced ICD augments antitumor immunity elicited by pd0-L1 | 43  |
| Dinaciclib                          | PD-1         | Colorectal cancer; Bladder cancer | Simultaneous        | Dinaciclib-induced ICD augments antitumor immunity elicited by pd0-L1 | 44  |
| Cisplatin                           | PD-1         | NSCLC; Fibrosarcoma        | Sequential          | FDA-approved lorbisnetin treatment showed traits of ICD and was boosted in combination with PD-1 and CTLA-4 ICI | 45  |
| Vinorelbine, cyclophosphamide and S-FU | PD-1       | Breast cancer; lymphoma    | Simultaneous        | Combination treatment with these chemotherapies synergized with pd0-L1 | 46  |
| LTX-401                             | PD-1 + CTLA-4| NSCLC; Fibrosarcoma        | Sequential          | LTX-401 treatment sequentially combined with double ICI exhibited strong abscopal antineoplastic effects | 47  |
| Local anesthetics in combination with cisplatin | PD-1 | Fibrosarcoma; breast cancer; colorectal cancer | Sequential          | Local anesthetics induce ICD and exert synergistic anticancer effect with cisplatin and pd0-L1 | 48  |
| Cold atmospheric plasma             | PD-L1        | Melanoma                   | Simultaneous        | Cold atmospheric plasma eicits ICD in melanoma and augments the antitumor effect of pd0-L1 | 49  |
| Radiotherapy                        | PD-1         | NSCLC                      | Sequential          | Radiotherapy potentiates the effect of pd0-L1 in KRAS-driven mouse NSCLC | 50  |
| Oncolytic virotherapy               | PD-1         | Breast cancer              | Sequential          | Oncolytic adenoviruses synergistically enhance anti-PD-L1 and anti-CTLA-4 immunotherapy | 51  |
| Local anesthetics in combination with cisplatin | PD-1 | Fibrosarcoma; breast cancer; colorectal cancer | Sequential          | Local anesthetics induce ICD and exert synergistic anticancer effect with cisplatin and pd0-L1 | 52  |

S-fluorouracil, S-FU; anaplastic large cell lymphoma, ALCL; caloric restriction mimics, CRM; chimeric antigen receptor-T cell, CAR-T; immune checkpoint inhibitor, IC; immunogenic cell death, ICD; Lewis lung carcinoma, LLC; non-small cell lung cancer, NSCLC
Table 2. Results from the Keynote-062 study and the Checkmate 649 study.

|                      | Keynote 062 | Checkmate 649 |
|----------------------|-------------|---------------|
|                      | aPD-1 + Chemo (n = 257) | Chemo (n = 250) | HR | P | aPD-1 + Chemo (n = 789) | Chemo (n = 792) | HR | P |
| Age, median (range)  | 62 (22–83)  | 63 (23–87)    |     |   | 62 (54–69)  | 61 (53–68)    |     |   |
| Sex (%)              |             |               |     |   |             |               |     |   |
| Men                  | 76          | 72            |     |   | 68          | 71            |     |   |
| Women                | 24          | 28            |     |   | 32          | 29            |     |   |
| Region (%)           |             |               |     |   |             |               |     |   |
| Asia                 | 25          | 24            |     |   | 23          | 22            |     |   |
| Others               | 75          | 76            |     |   | 77          | 78            |     |   |
| ECOG (%)             |             |               |     |   |             |               |     |   |
| 0                    | 46          | 46            |     |   | 41          | 42            |     |   |
| 1                    | 54          | 54            |     |   | 59          | 57            |     |   |
| Location (%)         |             |               |     |   |             |               |     |   |
| Stomach              | 66          | 72            |     |   | 70          | 70            |     |   |
| GEJ/E                | 33          | 27            |     |   | 30          | 30            |     |   |
| Metastatic           |             |               |     |   |             |               |     |   |
| PD-L1 CPS (%)        |             |               |     |   |             |               |     |   |
| ≥ 1                  | 100         | 100           |     |   | 81          | 83            |     |   |
| ≥ 5                  |              |               |     |   | 60          | 61            |     |   |
| ≥ 10                 | 39          | 36            |     |   | 3            | 3             |     |   |
| MSI-H (%)            | 7           | 8             |     |   | 3           | 3             |     |   |
| Chemo                |             |               |     |   |             |               |     |   |
| Platinum             | Cisplatin   | Oxaliplatin   |     |   |             |               |     |   |
| S-Fu ± LV (%)        | 38          | 38            |     |   | 54          | 53            |     |   |
| Capecitabine (%)     | 62          | 62            |     |   | 46          | 47            |     |   |
| aPD-1                |             |               |     |   |             |               |     |   |
| Median OS (month)    |             |               |     |   |             |               |     |   |
| PD-L1 CPS ≥ 1        | 12.5        | 11.1          | 0.85 | 0.05 | 14.0        | 11.3          | 0.77 | < 0.0001 |
| PD-L1 CPS ≥ 5        | 12.3        | 10.8          | 0.85 | 0.16 | 14.4        | 11.1          | 0.71 | < 0.0001 |
| 1-year OS (%)        |             |               |     |   |             |               |     |   |
| PD-L1 CPS ≥ 1        | 53          | 46            |     |   | 56          | 47            |     |   |
| PD-L1 CPS ≥ 5        |              |               |     |   | 57          | 46            |     |   |
| Median PFS (month)   |             |               |     |   |             |               |     |   |
| PD-L1 CPS ≥ 1        | 6.9         | 6.4           | 0.84 | 0.04 | 7.5         | 6.9           | 0.74 |     |
| PD-L1 CPS ≥ 5        |              |               |     |   | 7.7         | 6.1           | 0.68 | < 0.0001 |
| PD-L1 CPS ≥ 10       |             |               |     |   |             |               |     |   |
| ORR rate (%)         |             |               |     |   |             |               |     |   |
| PD-L1 CPS ≥ 1        | 49          | 37            |     |   | 60          | 46            |     |   |
| PD-L1 CPS ≥ 5        |              |               |     |   | 60          | 45            |     |   |
| PD-L1 CPS ≥ 10       | 53          | 38            |     |   | 59          | 44            |     |   |
| Toxicity G3-G4 (%)   | 73          | 69            |     |   |             |               |     |   |

S-fluorouracil, S-FU; combined positive score, CPS; eastern cooperative oncology group, ECOG; gastroesophageal junction/esophagus, GEJ/E; Hazard ratio, HR; leucovorin, LV; objective response rate, ORR; overall survival, OS; progression-free survival, PFS

trial. More importantly, the ORR improvement was more profound in patients receiving oxaliplatin (24.3%) than in those treated with cisplatin (11.8%), again supporting the superiority of oxaliplatin over cisplatin.

Other ongoing clinical trials that combine oxaliplatin or cisplatin with PD-1/PD-L1 blockade are summarized in Table 3. It is increasingly acknowledged that platinum drugs differ in their capacity to induce ICD and only those that trigger ICD are able to synergize with ICI. Oxaliplatin is used as the backbone of chemotherapy for gastric cancer in the majority of ongoing-phase II/III trials. Nonetheless, a substantial number of trials still include cisplatin in their chemotherapy regimen as equivalent or substitute for oxaliplatin in a few phase II studies. Similarly, there are no specifications on which type of platinum agent to combine with PD-1 blockade for first-line treatment of gastric cancer in the FDA approval, which vaguely refers to ‘platinum-based chemotherapy’ without distinguishing between cisplatin and oxaliplatin.

In sum, it is still not fully appreciated by regulatory instances including FDA and EMA that different platinum drugs have distinct immunogenic properties and that it is crucial to use ICD inducing agents such as oxaliplatin when the purpose of combinational treatment is to trigger anti-tumor immune response. At this point, we strongly recommend that future clinical studies, as well as ongoing trials that are still in the stage of recruiting patients, should consider the optimization of treatment regimes in which immunogenic chemotherapy should be used during one or few cycles at relatively low doses (to avoid the adverse effects that have been observed during high-dose monotherapy schedules) as a preconditioning of the tumor immune microenvironment for subsequent curative ICI.

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Table 3. List of ongoing clinical trials that evaluate the combination of PD-1/PD-L1 blockade with either cisplatin or oxaliplatin in gastric cancer.

| NCT Number        | Trial phase | Patient enrollment | IC target | Platinum                |
|-------------------|-------------|--------------------|-----------|-------------------------|
| NCT03675737       | Phase 3     | 1579               | PD-1      | Cisplatin or Oxaliplatin|
| NCT03221426       | Phase 3     | 1007               | PD-1      | Cisplatin or Oxaliplatin|
| NCT03615326       | Phase 3     | 732                | PD-1      | Cisplatin or Oxaliplatin|
| NCT01802241       | Phase 3     | 120                | PD-1      | Cisplatin or Oxaliplatin|
| NCT01512147       | Phase 3     | 714                | PD-1      | Cisplatin or Oxaliplatin|
| NCT03813784       | Phase 3     | 887                | PD-1      | Oxaliplatin             |
| NCT03745170       | Phase 3     | 650                | PD-1      | Oxaliplatin             |
| NCT02872116       | Phase 3     | 2031               | PD-1      | Oxaliplatin             |
| NCT04139135       | Phase 3     | 642                | PD-1      | Oxaliplatin             |
| NCT04997837       | Phase 3     | 433                | PD-1      | Oxaliplatin             |
| NCT05180734       | Phase 3     | 680                | PD-1      | Oxaliplatin             |
| NCT04950322       | Phase 3     | 920                | PD-L1     | Oxaliplatin             |
| NCT05149807       | Phase 2/3   | 896                | PD-L1     | Oxaliplatin             |
| NCT05325528       | Phase 2/3   | 40                 | PD-1      | Oxaliplatin             |
| NCT05002666       | Phase 2/3   | 60                 | PD-1      | Oxaliplatin             |
| NCT05313906       | Phase 2     | 40                 | PD-1      | Cisplatin               |
| NCT04249739       | Phase 2     | 93                 | PD-1      | Cisplatin               |
| NCT03939962       | Phase 2     | 60                 | PD-1      | Oxaliplatin             |
| NCT04367025       | Phase 2     | 70                 | PD-1      | Oxaliplatin             |
| NCT05177068       | Phase 2     | 42                 | PD-1      | Oxaliplatin             |
| NCT05239766       | Phase 2     | 120                | PD-1      | Oxaliplatin             |
| NCT04819971       | Phase 2     | 67                 | PD-1      | Oxaliplatin             |
| NCT03878472       | Phase 2     | 30                 | PD-1      | Oxaliplatin             |
| NCT04250948       | Phase 2     | 108                | PD-1      | Oxaliplatin             |
| NCT04890392       | Phase 2     | 20                 | PD-1      | Oxaliplatin             |
| NCT04510064       | Phase 2     | 40                 | PD-1      | Oxaliplatin             |
| NCT03950271       | Phase 2     | 25                 | PD-1      | Oxaliplatin             |
| NCT05246982       | Phase 2     | 40                 | PD-1      | Oxaliplatin             |
| NCT04744649       | Phase 2     | 80                 | PD-1      | Oxaliplatin             |
| NCT05223088       | Phase 2     | 40                 | PD-1      | Oxaliplatin             |
| NCT05033392       | Phase 2     | 62                 | PD-1      | Oxaliplatin             |
| NCT04354662       | Phase 2     | 35                 | PD-1      | Oxaliplatin             |
| NCT05000554       | Phase 2     | 30                 | PD-1      | Oxaliplatin             |
| NCT05161572       | Phase 2     | 152                | PD-1      | Oxaliplatin             |
| NCT04119622       | Phase 2     | 30                 | PD-1      | Oxaliplatin             |
| NCT07499548       | Phase 2     | 71                 | PD-1      | Oxaliplatin             |
| NCT05216237       | Phase 2     | 31                 | PD-1      | Oxaliplatin             |
| NCT04694183       | Phase 2     | 60                 | PD-1      | Oxaliplatin             |
| NCT04661150       | Phase 2     | 52                 | PD-L1     | Oxaliplatin             |
| NCT04933227       | Phase 2     | 60                 | PD-L1     | Oxaliplatin             |
| NCT03299071       | Phase 2     | 40                 | PD-L1     | Oxaliplatin             |
| NCT03488667       | Phase 2     | 40                 | PD-1      | Oxaliplatin             |
| NCT03647969       | Phase 2     | 257                | PD-1      | Oxaliplatin             |
| NCT04065282       | Phase 2     | 36                 | PD-1      | Oxaliplatin             |
| NCT02901301       | Phase 1/2   | 41                 | PD-1      | Cisplatin               |
| NCT03852251       | Phase 1/2   | 112                | PD-1      | Cisplatin or Oxaliplatin|

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