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Immunotherapy for Gestational Trophoblastic Neoplasia: A New Paradigm

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Keywords
Immune checkpoint immunotherapy · Gestational trophoblastic neoplasia · Multidrug resistance · (Inter)national treatment guidelines

Abstract

Background: Immune checkpoint immunotherapy (CPI) targeting programmed cell death 1 (PD-1)/ligand (PD-L1) has been shown to be an effective treatment for gestational trophoblastic neoplasia (GTN). This includes those with multidrug resistance, ultra-high-risk disease, and epithelioid trophoblastic tumour/placental site trophoblastic tumour subtypes that are inherently chemotherapy resistant, but there is also emerging evidence in low-risk disease. ***Objectives:*** We set out to generate an overview of the current data supporting the use of CPI for GTN in both high-risk and low-risk disease and to consider future research goals and directions in order to implement CPI in current treatment guidelines. ***Methods:*** We identified and reviewed the published data on the use of CPI agents in GTN. ***Outcome:*** 133 patients were identified who had been treated with CPI for GTN with pembrolizumab (23), avelumab (22), camrelizumab (57), toripalimab (15), or other anti-PD-1 agents (16), of whom 118 had high-risk diseases, relapse or multi-drug resistant disease, and 15 low-risk diseases. Overall 85 patients achieved complete remission, 77 (of 118) with high-risk disease, and 8 (of 15) with low-risk disease. 1 patient with complete remission in the high-risk group developed a relapse 22 months after anti-PD-1 treatment had been stopped. Treatment was generally well tolerated across studies. ***Conclusions and Outlook:*** The majority of high-risk patients (77/118) treated with CPI are cured and this is particularly relevant amongst those with chemotherapy resistant disease who otherwise have very limited treatment options. Priorities for future research include determining whether these agents have a role earlier in the disease course, the utility of combination with chemotherapy, and effects on future fertility. Treatment availability remains a concern due to the high price of these agents.

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Introduction

Most patients with gestational trophoblastic neoplasia (GTN) are cured with surgery, chemotherapy, or both, but certain GTN subsets have been associated with a significantly elevated risk of treatment failure and death. Two groups of patients have worse outcomes due to the development of multidrug resistant disease: patients with risk factors including liver with or without brain metastases, defined as ultra-high risk, usually with a FIGO score of 13 or more [1, 2]; secondly, patients with the rare epithelioid trophoblastic tumour (ETT) and placental site trophoblastic tumour (PSTT) subtypes are inherently more chemo-resistant. Patients in this group with stage IV disease or who present more than 4 years from the end of their antecedent or causative pregnancy regardless of stage have significantly worse outcomes [3–5]; long interval disease has a survival rate of 48% even with aggressive platinum-based chemotherapy including high-dose treatment with stem cell support [4].

Over the past decade, immune checkpoint immunotherapy (CPI) with agents targeting inhibitory T cell receptors including programmed cell death 1 (PD-1) and its ligand (PD-L1) and cytotoxic T-lymphocyte associated antigen 4, have revolutionised the treatment of several types of cancer such as melanoma [6], non-small cell lung cancer [7] and renal cell cancer [8]. Whilst the precise mechanisms of action remain incompletely understood, CPIs in general enhance the functional capability of the T-cell response.

GTN has multiple features that predict responsiveness to CPI. Firstly, in other cancer types, the success of CPI has been related to cancer cell antigenicity, measured as the quantity [9] or quality [10] of MHC class I presented antigens. GTN is unique in arising from non-self-cells since the placental trophoblast is semi-allogeneic genomically, thus predicted to be highly antigenic. Secondly, a pre-existing immune infiltrate is a predictor of CPI outcome across cancer types [11–13] and GTN is usually richly immune infiltrated [14–16]. Thirdly, expression of the PD-1 ligand PD-L1 has been related to CPI response, and malignant trophoblast cells strongly express this marker [14, 17, 18]. Finally, animal studies show foetal wastage upon anti-PD-L1 treatment of pregnant mice in the context of allogeneic pregnancy [19].

Based on these data, it was first shown in 2017 that patients with drug resistant GTN can be cured with anti-PD-1 therapy [20]. This has paved the way for further studies suggesting the utility of immunotherapy earlier in the treatment course [21].

In GTN, work has focused on agents that block PD-1 (e.g., pembrolizumab [20], toripalimab [22] and camrelizumab [23]) or the tumour and immune cell expressed PD-L1 (e.g., avelumab [21, 24]). In this review, we discuss the current data supporting the use of CPIs for GTN and future directions.

Immunotherapy for Patients with High-Risk, Chemotherapy Insensitive Disease

Table 1 provides an overview of the currently reported cases of GTN in the literature that have been treated with a CPI – a total of 133 patients, most of them with multidrug resistant disease. Patients with multidrug resistant GTN historically have an exceptionally poor prognosis and pembrolizumab was the first agent to demonstrate the potential for complete remissions in this group. The first report of pembrolizumab used to treat GTN was published in 2017 and described 4 patients with progressive high-risk disease after treatment with polychemotherapy [20]. After several lines of chemotherapy, these 4 patients (2 with choriocarcinoma, 1 with PSTT, and 1 with a mixed tumour of PSTT and ETT) all received pembrolizumab. Three patients achieved a complete response and remained in remission. One patient unfortunately progressed and subsequently died of her disease.

Based on these clinical data, UK guidelines were put in place to offer pembrolizumab to patients with high-risk disease (FIGO score of 7 or more) who have failed 2 lines of multi-agent chemotherapy including 1st line EMA/CO [35]. It was also made available for poor prognosis PSTT/ETT cases after first-line platinum-based chemotherapy with EP/EMA or TE/TP instead of using high-dose chemotherapy. During the COVID-19 pandemic, these guidelines were updated to allow access to pembrolizumab after failure of 1st line EMA/CO only and instead of EP/EMA chemotherapy in PSTT/ETT cases. UK guidelines currently recommend treatment until hCG normalisation or radiological disease resolution (if hCG is not elevated at the beginning of therapy), followed by 5 consolidation cycles in high-risk GTN and for a total of 6 months in the adjuvant setting post-hysterectomy for PSTT/ETT.

Multiple small studies supporting the efficacy and low toxicity of CPIs in GTN have subsequently been published from multiple centres (Table 1). The majority are case reports or small series of patients with multidrug resistant GTN, but evidence for the use of CPIs in an earlier setting, e.g., low-risk disease resistant to single-agent chemotherapy, is emerging [21]. Most patients have been treated with pembrolizumab, but other anti-PD1 agents have been successfully used [21–24].

We found 12 single-case reports of patients with multidrug resistant GTN that were treated with pembrolizumab (Table 1). Across these reports, 11 out of 12

Table 1. Current summary of reported patients with GTN treated with CPI

Study	Type of study	Patients, *n*	Diagnosis	Clinical setting	Therapeutic agent	Outcome	Grade 3 or 4 toxicity
Ghorani et al. [20] (2017)	Clinical case report	4	2 choriocarcinoma 1 PSTT 1 PSTT/ETT mixed type	Multidrug resistant disease	Pembrolizumab	3 CR, 1 PD	No
Huang et al. [25] (2017)	Clinical case report	1	Choriocarcinoma	Multidrug resistant disease	Pembrolizumab	CR	Grade 3 transaminitis
Choi et al. [26] (2019)	Clinical case report	2	1 PSTT 1 ETT Both tumours dMMR	Multidrug resistant disease	Pembrolizumab	CR	No
Cheng et al. [27] (2020)	Clinical case report	8	7 choriocarcinoma 1 ETT (abstract only, paper in Chinese)	Multidrug resistant disease	Unknown (anti-PD-1)	4 CR 4 relapsed, different systemic treatment, no follow-up information	No
Goldfarb et al. [28] (2020)	Clinical case report	1	Choriocarcinoma	Multidrug resistant disease	Pembrolizumab	CR but relapse after 22 months, pembro reinstalled, no follow-up information	Grade 3 neuropathy
Clair et al. [29] (2020)	Clinical case report	1	Choriocarcinoma	Multidrug resistant disease	Pembrolizumab	CR	Unknown
Bell et al. [30] (2021)	Clinical case report	1	ETT	Multidrug resistant disease	Pembrolizumab	CR	Unknown
Paspalj et al. [31] (2021)	Clinical case report	1	Choriocarcinoma	Multidrug resistant disease	Pembrolizumab	CR	No
Pisani et al. [32] (2021)	Clinical case report	1	ETT	Multidrug resistant disease	Pembrolizumab	CR	No
Cheng et al. [23] (2021)	Prospective phase II trial	20	19 choriocarcinoma 1 PSTT	High-risk (FIGO>7) chemotherapy refractory or relapsed GTN	Camrelizumab and Apatinib	10 CR 10 PD and received multi-modality treatment	12 patients grade 3 toxicities
You et al. [21] (2020)	Prospective phase II trial	15	Low-risk GTN	GTN progressive after single-agent chemotherapy	Avelumab	8 CR (and 1 healthy pregnancy post treatment) 7 PD, reached CR after Act-D or multi-modality treatment	No

Table 1 (continued)

Study	Type of study	Patients, *n*	Diagnosis	Clinical setting	Therapeutic agent	Outcome	Grade 3 or 4 toxicity
Posnaszek et al. [33] (2021)	Clinical case report	1	PSTT	Uterine tumour, patient declined surgery and chemotherapy	Pembrolizumab	CR after 3 cycles (and healthy pregnancy after treatment)	Unknown
You et al. [24] (2023)	Prospective phase II trial	7	High-risk GTN	Multidrug resistant disease	Avelumab	1 CR 6 PD, study stopped for futility	No
Liu et al. [22] (2022)	Clinical case report	4	1 GTN not specified 3 choriocarcinoma	Multidrug resistant disease	Toripalimab combined with chemotherapy	4 CR	No
Wang et al. [34] (2023)	Retrospective cohort study	66	59 choriocarcinoma 7 PSTT/ETT	Chemo-refractory or relapsed GTN (all FIGO score >7)	Camrelizumab (37) Sintilimab (8) Toripalimab (11) Pembrolizumab (10)[1]	CR 46 PR 6 No response 14	25 patients[2]

TKI, tyrosine kinase inhibitor. [1]In 31 patients, CPI was combined with different schedules of chemotherapy; 20 patients received apatinib (TKI) in addition to anti-PD-1 therapy. [2]25 (of 66) patients with grade 3–4 toxicity reported received; anti-PD1 only: 10 patients (out of 35); anti-PD-1 plus chemotherapy: 15 (out of 31).

patients with multidrug resistant disease went on to have hCG normalisation after treatment with pembrolizumab (Table 1). One of these 11 patients developed a relapse after 22 months, for which pembrolizumab was restarted [28], but further clinical data are unavailable. One patient had progressive disease and died [20].

The majority of reported patients had PD-L1 expression of >90% and treatment was well tolerated throughout. Unpublished data presented at the XXI World ISSTD Congress in October 2022 on an international cohort of an additional 58 cases further supports the observation that a majority of drug resistant patients are cured with pembrolizumab and demonstrate durability of responses [36].

Other anti-PD1 agents have also shown signs of efficacy. In a single-arm phase II study of 20 patients with high-risk chemo-resistant or relapsed GTN [23], Cheng et al. assessed the use of the anti-PD1 agent camrelizumab, licensed in China, plus the tyrosine kinase inhibitor apatinib which has high specificity for vascular endothelial growth factor (VEGF) receptor 2 signalling. In this cohort, 11 of 20 patients showed an objective response (response rate 55%) with 10 patients achieving complete response. Nine patients discontinued study treatment and received salvage chemotherapy after progressive disease. Interestingly, 7 of these 9 patients showed a complete response after salvage chemotherapy, including 5 patients for whom the same chemotherapy regimen was unsuccessful before enrolment [23]. This might suggest a potential effect of anti-PD-1 therapy on chemo-resistance and raises a question for exploring the combination of CPIs with chemotherapy. In this study, the additional benefit of apatinib over a PD-1 inhibitor alone is unclear since there was no control arm with apatinib monotherapy and outcomes are similar to what has been reported with anti-PD-1 therapy alone. In general, VEGF signalling is associated with endothelial anergy [37] and loss of adhesion molecules required for T cell trafficking into the tumour microenvironment, with anti-VEGF/CPI combination therapy predicted to be most effective for tumours without a pre-existing immune infiltrate, unlike what is usually observed in GTN. Further study is required to assess the effectivity of camrelizumab as monotherapy for GTN.

Liu et al. [22] reported a series of 4 patients with multidrug resistant disease who were all treated with the anti-PD-1 agent toripalimab (Table 1). Toripalimab was not given as monotherapy but combined with chemotherapy in all 4 patients (1 patient received nab-paclitaxel

and bevacizumab with toripalimab, the other 3 patients paclitaxel and cisplatin). Therefore, no conclusions considering the effectivity of toripalimab as single-agent therapy can be drawn. All 4 patients achieved complete remission after treatment with toripalimab combined with chemotherapy. Treatment was well tolerated.

Wang et al. [34] recently reported a retrospective cohort study of 66 patients with chemo-refractory high-risk GTN. The patients in this study were treated with 4 different anti-PD-1 antibodies (Table 1). In 31 patients, CPI was combined with various chemotherapy schedules. CPI was combined with apatinib in 20 of 35 patients without chemotherapy (Table 1) [34].

In this study, 46 of 66 patients reached a complete remission after anti-PD-1 therapy with or without chemotherapy or apatinib. 17 patients in the CPI monotherapy group received salvage chemotherapy because of progressive disease, of whom 12 subsequently achieved a CR. Because of the range of different therapies and combination therapies given, it is difficult to draw a conclusion on what was the most effective treatment strategy in this study, but the efficacy of CPI is clearly reiterated. The relatively elevated rate of grade 3–4 toxicity ($n = 25/66$) in comparison to other studies is likely due to combination with multiple chemotherapy schedules or apatinib (Table 1).

Not all CPIs have proven to be effective in the treatment of high-risk multidrug resistant GTN. Evidence from Arm B of the French TROPHIMMUN study [24] suggests that the anti-PD-L1 targeted agent avelumab has low activity in this setting. In this study, 7 patients with high-risk multidrug resistant GTN were treated with avelumab. Just 1 patient achieved remission and the trial was stopped due to futility.

Immunotherapy in Low-Risk Disease

Patients with a FIGO score of under 7 are usually cured with one or two sequential single-agent chemotherapy agents (methotrexate and actinomycin-D). However, the proportion cured in this way falls as the FIGO score rises. Thus, 40% of patients with a FIGO score of 5 or 6 will eventually require more toxic combination agent chemotherapy to achieve remission [38]. Given the efficacy and low toxicity of CPIs, there is interest in determining whether these agents can be introduced at resistance to single-agent chemotherapy.

This concept was first tested in the recent TROPHIMMUN trial [21]. In this single-arm phase II trial, 15 patients with low-risk disease resistant to single-agent methotrexate were treated with avelumab. Amongst this group, eight (53%) achieved a durable complete response, of whom 5 would otherwise have received polychemotherapy which was avoided by the use of avelumab. Of those who failed immunotherapy, three were cured with single-agent actinomycin-D, three with multi-agent chemotherapy, and one with hysterectomy. Thus avelumab may be an option for patients who fail single-agent chemotherapy and wish to avoid more toxic multi-agent treatment.

Several other studies are evaluating the possibility of introducing earlier CPI treatment of GTN, including the TROPHAMET study (NCT04396223) evaluating the use of combined methotrexate and avelumab in low-risk GTN as a first-line treatment [21], the RESOLVE study (NCT05635344) of neoadjuvant pembrolizumab prior to second evacuation of post-molar GTN and the AVOCADO study [39] which will offer combination pembrolizumab and actinomycin-D for patients who fail methotrexate or methotrexate and sequential actinomycin-D.

Adverse Events

In general, toxicities with CPIs are substantially lower than with combination agent chemotherapies. Amongst patients with GTN, published data suggest a low toxicity rate with few grade 3/4 events. For the 133 patients assembled in Table 1, information on toxicity could be retrieved for 130. Except for the study of Wang et al. which included patients treated with apatanib or chemotherapy [34], there were no grade 4 toxicities. A higher grade 3–4 toxicity rate was seen in the CAP01 study of camrelizumab and apatinib [23]. Twelve of 20 patients in the camrelizumab and apatinib study [23] had various grade 3 toxicities. The most common grade 3 toxicity was hypertension, which was attributable to apatinib. The toxicity of camrelizumab as monotherapy cannot be assessed from this study since all patients were treated with combination therapy. Because of the different combination therapy schedules in the study by Wang et al. [34], toxicity in this cohort is very difficult to interpret.

For the remaining 44 patients who were treated with CPI monotherapy, only 2 cases of grade 3 toxicity were reported; 1 case of transaminitis [25] and one of peripheral neuropathy [28]. This represents approximately only 3% of cases treated with CPI monotherapy, as summarised in Table 1 for those for whom data on toxicity is available.

Of note, the patient with transaminitis was treated with steroids and her transaminases normalised in just 1 week. After this, pembrolizumab treatment was continued with a 2 week delay without recurrence of toxicity, and thus was not clinically significant. The other patient with grade 3 toxicity suffered from peripheral neuropathy. This can be caused by

CPIs but is relatively uncommon. Before starting her CPI treatment, this patient received polychemotherapy including multiple neurotoxic agents including vincristine, platinum, and paclitaxel, which could also account for the neuropathy.

Fertility

In terms of future fertility, CPIs are theoretically associated with endocrine disorders affecting reproductive functions in women. Severe auto-immune adverse events such as hypothyroidism and hypophysitis induced by CPIs may be involved in infertility, although to date no definitive sterility was reported after such adverse events. Moreover, several deliveries after anti-PD-1 (nivolumab) and anti-cytotoxic T-lymphocyte associated antigen-4 (ipilimumab) given as treatment for melanoma have been reported [40–44]. Concerning GTN, preliminary data from the French group presented at the XXI World ISSTD Congress 2022 show that among 42 patients previously treated by anti-PD-L1 (avelumab), 13 attempted to achieve pregnancy after avelumab, of whom 7 delivered at term, 3 miscarried and 3 are currently trying to conceive. After pembrolizumab, only 1 case report of safe term delivery was published on a patient who received three 200 mg doses for a FIGO Stage I PSTT and was considered cured [33]. Long-term follow-up for this patient is unfortunately not available. Although this is reassuring, it will take further study and international collaboration to gain insights into the long-term effects of CPIs on future fertility in general and GTN patients in particular. To date, it seems that the minimum requirement for a woman starting a pregnancy after CPI therapy is close monitoring of maternal endocrine function and foetal growth during pregnancy.

Financial Toxicity/Reimbursement

Timely CPI treatment initiation is considered imperative amongst patients with chemotherapy resistant disease. However, CPIs are costly and in general not affordable for hospitals and patients unless reimbursed. Considering the rarity of GTN in general and the even rarer incidence of patients requiring immunotherapy, the current experience and literature should suffice to prompt health insurance companies to reimburse treatment costs. Unfortunately, in many countries, this is not yet the case. In the Netherlands, e.g., there is currently no reimbursement for CPIs in GTN and funding must be sought on a case-by-case basis. The UK guideline [35] has proven to be very helpful in negotiating this. In France, avelumab is available through a compassionate access scheme and is offered to low-risk patients who have failed single-agent chemotherapy, as an alternative to multi-agent treatment. Pembrolizumab can be prescribed off-label provided the hospital covers the cost.

Incorporating Immunotherapy into Current Guidelines

Historically, given the rarity of the disease, progress in management of GTN has been driven by data from non-randomised studies and the current standards of care in GTN in general and high-risk disease in particular were established primarily by analysis of retrospective cohorts treated at reference centres [45]. Noting the limitations of the currently available data, anti-PD-1 therapy with multiple agents has emerged across centres as the only therapy capable of curing patients with multidrug resistant GTN. Patients in this category would previously have been offered phase I trials or best supportive care having exhausted standard chemotherapy options, but now have a good chance of achieving remission.

Considering the inherent limitations of the current evidence base and trials in this area, anti-PD-1 therapy is now considered a standard of care for patients with multidrug resistant GTN. Whilst randomised studies are desirable, a non-immunotherapy control arm would be unethical given the high cure rate observed across multiple studies, although collection of prospective data is warranted. A phase II Korean study (NCT04303884) is currently in setup to explore outcomes of patients with drug resistant GTN treated with pembrolizumab.

Priorities for Future Clinical Research

For patients with GTN, immune checkpoint inhibitors offer an effective therapy with a high cure rate and relatively low toxicity. When and how this new modality should be implemented in current guidelines is a challenge that needs to be addressed internationally. Several areas remain insufficiently well explored and can be identified as priorities for future research.

Adjuvant immunotherapy is a priority area for research. Patients with ETT/PSTT and a long duration between diagnosis and antecedent pregnancy have a particularly poor prognosis even when the disease can be surgically resected [3]. Whilst outcomes have improved with multi-agent adjuvant chemotherapy and high-dose chemotherapy, there remains much room for improvement. These regimens are of high toxicity. There is ongoing interest in whether adjuvant pembrolizumab can be used instead of

chemotherapy, and a number of patients have been treated to date as presented by the Charing Cross Hospital group at the XXI World ISSTD Congress 2022. However, given the rarity of the condition and the need for a long follow-up period, a much larger international collaboration is required to test the utility of immunotherapy in this setting.

Combination chemotherapy is an area of interest. In other cancer types, synergistic effects of chemo-immunotherapy combinations have been shown [46, 47]. The retrospective cohort described by Wang [34] suggests an improved anti-tumour effect in high-risk chemo-refractory GTN for anti-PD1 combined with chemotherapy. Similarly, our groups have noted the potential for more rapid responses amongst patients treated with chemo-immunotherapy versus immunotherapy alone, but it is not clear what effect this may have on cure rates and survival outcomes. In general, combination therapy may result in a reduction in the duration of chemotherapy required to achieve cure and therefore potentially less toxicity.

Immunotherapy offers a new modality to integrate into existing treatment pathways and future work should focus on how best to do this. For instance, studies such as TROPHAMET, RESOLVE, and AVOCADO are ongoing or in setup to determine whether immunotherapy can be introduced earlier in the treatment course for both patients with high- and low-risk disease and to what extent immunotherapy may be used as a chemotherapy sparing agent to reduce toxicities.

Predictors of outcome to CPI therapy are currently not well known. Whilst most patients with multidrug resistance respond to anti-PD-1 therapy, a proportion of patients fail. This has been associated with lack of tumour infiltrating lymphocytes consistent with other studies, suggesting the importance of a pre-existing immune response or a microenvironment capable of supporting T-cell infiltration [20]. Absent expression of the non-classical MHC class I protein HLA-G which has immunomodulatory properties [48] may also be a predictor. Further work is required to better understand immunotherapy resistance and develop strategies to treat patients who do not respond.

Finally, further longitudinal studies are required to determine if immunotherapy has any long-term consequences particularly on fertility. Whilst there is a theoretical risk of impaired future fertility, any impact is currently unknown. Of special concern is the (long-term) effect of the immune response directed against trophoblastic cells when CPIs are given for GTN. Multiple case reports of patients becoming pregnant unexpectedly during immunotherapy suggest women are able to achieve normal pregnancy outcomes despite treatment with CPIs [21, 33, 40–44, 49, 50].

Conclusion

CPI offers a valuable new treatment modality in GTN and opens opportunities for a re-evaluation of established treatment guidelines. Whilst anti-PD-1 salvage treatment in multidrug resistant disease is now a standard of care, given the efficacy and relatively low toxicity, immune checkpoint inhibitors could also offer opportunities to avoid or reduce the use of (multi-agent) chemotherapy regimens, resulting in less toxicity and better quality of life.

There remain many questions which will require international collaboration to solve, given the rare nature of this disease. Across cancer types, data on long-term toxicity and fertility is scarce. Given the nature of the patients involved, careful evaluation of long-term fertility outcomes in particular is required since treatment with immune checkpoint inhibitors enhances immune responses against trophoblast cells.

As there are a limited number of small immunotherapy trials in GTN, and these have used a variety of agents, it is unclear whether there are drug specific differences in efficacy. Studies including TROPHAMET, RESOLVE, AVOCADO, and others will address how immunotherapy can be used to cure more patients with less toxicity and should reveal whether there are any longer term toxicity issues in this young female population. Furthermore, it should be a prime concern for medical professionals and their (inter)national organisations involved in the management of GTN as well as for governments and pharmacological manufacturers to ensure availability of CPIs for all those GTN patients who may benefit from it.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

I.O.B. identified and analysed published data on the use of CPI agents in GTN. I.O.B. and E.G. wrote the manuscript with input and revisions from A.M.W., B.Y., P.A.B., and M.J.S.

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