USE OF REPURPOSED DRUGS TO TARGET CANCER METABOLISM

A white paper that offers certain proprietary details about the first privately-funded initiative with the specific aim of repurposing and redeveloping old drugs for use in oncology and making them accessible to patients in a clinical setting.

- Travis Christofferson, MS
  Alexandra Dedman, PhD

CareOncology™
YOUR HOPE IS IN OUR CARE
Use of Repurposed Drugs to Target Cancer Metabolism

A white paper and literature review that offers certain confidential and proprietary details about the first privately-funded initiative with the specific aim of repurposing and redeveloping old drugs for use in oncology and making them accessible to patients in a clinical setting.

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About Care Oncology / Health Clinics Limited

Care Oncology Clinic (COC) was established in London, United Kingdom, in 2013. Care Oncology Clinic’s ambition is to be the leading global specialist centre of excellence in the clinical delivery of repurposed medicines to target cancer metabolism. COC has developed the COC Protocol™, a patented combination of medicines that targets the metabolism of cancer cells. COC is a division of Health Clinics Limited – a UK registered private limited company.

Cancer is a complex illness, with a heavy disease burden for patients, and our aim is to provide an effective adjunctive treatment safely. The administration of any medicines needs to be done from a specialist centre, which has expertise in the treatment of many of the different types of cancer, at all stages of the disease, and alongside the standard of care treatments employed.

The Care Oncology Clinic conducts multiple research programmes into the safety and efficacy of the COC Protocol™. The company also invests in drug development programmes – modifying and reformulating the drugs comprising the protocol to optimise them for use in cancer.

Where to access the treatment

The COC Protocol is provided in the United States by Health Clinics LLC, trading as Care Oncology. Care Oncology provides a telemedicine solution for patients nationwide.

For further information see www.careoncology.com or call 800-392-1353

Intended audience

This paper is the first in a series of scientific reviews and is intended for healthcare professionals, clinical researchers and scientists. It aims to provide a brief overview of the extensive scientific literature supporting the use of the COC Protocol™ in cancer.
**Intellectual Property**

The Care Oncology Clinic’s treatment is protected in the United States by patent US9622982B2 and there are patents issued and pending in multiple other jurisdictions.

The Care Oncology Clinic is committed to making the treatment broadly available and is actively recruiting partner clinics and physicians.

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Introduction to the concept of re-purposing

At least 2,000 drugs are now approved for marketing worldwide. Most of these drugs are only licensed for one or two different clinical conditions. Yet it is widely acknowledged that many approved drugs exhibit a high-degree of pleiotropy and can modulate more than one pathway within the cell. In fact, each drug on the market is estimated to have an average of around 6 different relevant molecular targets. This suggests significant unrealised potential within our existing drug-pool.

Occasionally one of these clinically relevant “off-target” effects will emerge serendipitously, giving the opportunity to “repurpose” the drug for the newly observed indication. This is how the unmistakable therapeutic benefits of Viagra® for erectile dysfunction were revealed during a Phase 1 trial for angina. And it is also how thalidomide, after a long and chequered history, eventually helped to change standard treatment for myeloma.

Repurposing lacks funding

But despite a few success stories, once a drug’s potentially advantageous off-target effects have been discovered, it remains extraordinarily difficult to translate this therapeutic benefit into the clinic. This is especially true for drugs which are off-patent, and/or their off-label effects have been widely published. Both of these characteristics reduce the chance of a pharmaceutical company recouping its costs of repurposing, and therefore can act as financial disincentives. As a result, many repositioned drugs are left stranded as “financial orphans”, and the potentially therapeutic benefits of repurposing low-cost, previously-licensed drugs remain relatively underexplored in the clinic. This is even the case in the context of oncology, where as many as 50 to 70% of all treatments are used off-label.

A new model of clinical research

A major expense of repurposing a drug for a different indication comes with financing the prospective randomized controlled Phase 3 trials (RCTs) needed to establish efficacy and safety. RCTs are a necessary part of the clinical development process and justifiably still considered the ‘gold-standard’ by drug authorisation agencies and the clinical community. However, there is increasing acknowledgement of the limitations of RCTs in effective translational research in selected areas. Features such as external validity and patient focus are often not prioritized in ‘gold-standard’ RCTs.

When weighing the evidence for clinical action, clinicians are required to consider carefully the quantity and validity of the data presented. This process can be further complicated when RCT results are not available for a new indication and can potentially block patient access to newly repurposed therapeutics which do not fit the standard clinical development model.

Despite the difficulties of repurposing off-patent drugs to treat alternative clinical indications, the potential benefit to patients is so obvious that this area has attracted substantial research interest from academic and non-profit organisations in recent years (for more information in this area, see www.ReDoProject.org, an international non-profit organization dedicated to accelerating the repurposing of drugs for use in oncology). However, with little financial backing, wider patient access to potentially therapeutically effective repurposed drugs in oncology remains limited.

Care Oncology bridges the gap
The UK-based Care Oncology Clinic is believed to be the first privately-funded initiative with the specific aim of repurposing and redeveloping old drugs for use in oncology and making them accessible to patients in a clinical setting. We believe that the risks and difficulties in prescribing medicines off-label in a systematic way are mitigated through delivery from a specialist centre.

We have established a clinical service underpinned by a carefully designed pluralistic research programme to provide patients with certain specific repositioned drugs which have solid evidence of safety and efficacy in cancer, with full support from our specialist doctors and oncologists. Our aim is to generate high quality clinical evidence demonstrating the anti-cancer impact of our selected medicines and their validity in clinical application, and to ensure these drugs are immediately available at a fair price to the patients who need them. Our approach is systematic and cautious, with the patient’s safety and wellbeing always to the fore.

Care Oncology Clinic’s therapeutic strategy looks to capitalise on the unique advantages of using repurposed drugs. These advantages include: the wealth of scientific knowledge which already exists for these drugs, their well-established safety profiles, and their affordability. Crucially, the detailed pharmacokinetic, pharmacovigilance, and safety data available for these drugs, along with extensive published research documenting their mechanisms-of-action, has enabled Care Oncology Clinic to develop the COC Protocol™.
The COC Protocol™

The COC Protocol™ is intended as an adjuvant treatment designed to work alongside, and not replace, a patients’ normal standard-of-care. At the core of the COC Protocol™ is a patented combination of four repurposed medications, each with extensive data supporting their potential as a metabolically-targeted adjunctive cancer treatment. Each drug has been selected based on the strength of evidence for anti-cancer activity, the established or predicted combinatorial action of the compounds, and their well-established safety records.

Patients attending the Care Oncology Clinic come under the care of clinicians with specialist knowledge of prescribing the COC Protocol medications in the context of cancer. Our clinicians will only recommend the COC Protocol to patients when they believe it will be safe, and beneficial to do so. Each COC Protocol prescription is tailored to the needs of the patient, and patients attending the clinic are carefully monitored for the duration of their treatment.

Why these four medications?

The COC Protocol is comprised of four repositioned drugs: atorvastatin, metformin, doxycycline, and mebendazole. Preclinical and mechanistic evidence supporting the use of these four drugs in combination as an adjuvant anti-cancer therapy is outlined below.

An anti-metabolic approach

Cancer cells are well known to exhibit metabolic dysregulation; relying on increased glucose metabolism and glycolysis to ensure their energy needs are met, despite the presence of oxygen (a phenomenon known as the Warburg effect). Positron emission tomography metabolic imaging studies reveal as many as 90% of all cancers exhibit characteristics of the Warburg effect¹⁰, and this near ubiquity has led to renewed interest in developing anti-cancer therapeutics which specifically target these characteristics¹¹,¹²

Existing evidence suggests that the four repositioned drugs which comprise the COC Protocol exert their anti-tumour effects through multiple overlapping direct and indirect effects. Direct effects include multi-targeted disruption of the cancer cell’s various dysregulated metabolic and non-metabolic pathways (see Table 1). Reported indirect effects include drug-induced immune system modulation¹³,¹⁴, and reduction in the overall availability of glucose and low-density lipoproteins to the cancer cell¹⁵,¹⁶.
Table 1: Individual COC Protocol medications target cancer in a number of different ways

<table>
<thead>
<tr>
<th>Anti-cancer mechanism of action</th>
<th>Evidence for COC Protocol components</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct actions</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Modulation of interconnected intracellular protein pathways involved in cancer cell growth, proliferation, apoptosis, and angiogenesis | Metformin<sup>17,18,19,20</sup>  
Statins<sup>21,22,23,24,25</sup>  
Mebendazole<sup>26,27,28,29,30,31,32,33</sup>  
Doxycycline<sup>34,35,36</sup> |
| Disruption of cancer cell membrane and signaling proteins and systems, including MMPs | Metformin<sup>37</sup>  
Statins<sup>38,39</sup>  
Doxycycline<sup>40,41</sup> |
| Epigenetic upregulation of apoptotic factors | Metformin<sup>42</sup> |
| Downregulation of oncogenic transcription factors such as STAT3 | Metformin<sup>43</sup>  
Doxycycline<sup>44</sup> |
| Disruption of the metabolic pathways of cancer stem cells | Metformin<sup>45,46</sup>  
Doxycycline<sup>47,48,49,50</sup> |
| **Indirect actions**            |                                       |
| Immune system modulation        | Statins<sup>51</sup>  
Mebendazole<sup>52</sup> |
| Reduction in availability of glucose and low-density lipoproteins to cancer cell | Metformin<sup>53</sup>  
Statins<sup>54</sup> |

NB Table 1 is a summary of the many different ways the COC Protocol medications have been shown to target cancer cells, as supported by published pre-clinical and mechanistic evidence. This list is not exhaustive.

**Multi-targeted activity**

Combination therapy is now considered a ‘cornerstone’ of effective cancer treatment<sup>55</sup>. Targeting multiple crucial cell pathways with a combination of agents, can enhance efficacy and reduce the potential for drug resistance to develop. There is also evidence that combining two or more compounds with alternative mechanisms of action can increase the success of drug repositioning<sup>56</sup>.

To develop the COC Protocol, our researchers comprehensively evaluated the known multi-target potential of each drug in terms of reported anti-cancer mechanism of action (Table 1), clinical and preclinical efficacy and safety, and also pharmacokinetic/pharmacodynamic activity. It is essential that each of these
parameters is considered when designing a combinative therapy. For example, many published studies on the clinical benefits of statins in cancer pooled lipophilic and hydrophilic statins together when analysing the data. However, analysis of preclinical studies reveals that the two classes of statins have very different pharmacodynamics. When the two classes of statins—lipophilic and hydrophilic—are separated, the superior anti-cancer activity of lipophilic statins become evident\(^5\) (there are well-established pharmacological reasons for this difference\(^5\)).

There is some pre-clinical evidence suggesting that metformin and lipophilic statins can have complementary mechanisms of action against cancer at the cellular level\(^60,61\). Both statins and metformin are highly pleiotropic small molecules and their reported complementary activity can in part be explained by the modification of multiple distinct and overlapping pathways that facilitate apoptosis, inhibit the cell cycle, reduce angiogenesis, and upregulate key oncogenic enzymes (see Table 1 and Figure 1).

Figure 1: Distinct and overlapping cancer cell pathways targeted by metformin and statins

NB: Figure 1 is based on evidence presented in the following references: 62,63,64,65.
An effective adjunct therapy

The COC Protocol is intended for use as an adjunctive therapy. The multi-targeted effects of the COC Protocol combined with well-established safety profiles for its individual components makes it ideally suited for this purpose. Indeed, substantial existing preclinical evidence supports the idea that the indirect and direct mechanistic effects outlined above serve to enhance the action of traditional cytotoxic therapies.

Furthermore, reducing the availability of glucose to cancer cells can potentiate the action of traditional cancer therapies through well-established mechanisms. For example, a reduction in glycolytic flux restricts the production of the intracellular antioxidant glutathione via downstream mechanisms. Less glutathione can render the cancer cell more vulnerable to oxidative cell death. Additionally, less access to glucose and reduced mitochondrial biogenesis results in less energy generation. This obviously impacts the cancer cell in many ways therapeutically, but critically, as an adjunct, it impacts the highly energy-dependent efflux pumps thus reducing the chance of developing resistance to cytotoxic therapy.

Taken together, this mechanistic evidence strongly suggests the COC Protocol components are a powerful sensitizer of cytotoxic therapies. However, good quality clinical data are needed to further strengthen this position.
Clinical data supporting use of the COC Protocol medications in cancer

Care Oncology retrospective data in glioblastoma patients

Care Oncology Clinic is deeply committed to evidence-based medicine and is working to gather high-quality real-world evidence of the safety, efficacy and optimum use of the COC Protocol in the adjuvant treatment of cancer. With this aim, we have developed METRICSplus, a long-term research strategy for gathering evidence from multiple complimentary sources, with the aim of triangulating and consolidating a clinically robust evidence base.

In the UK, the Medicines and Healthcare Products Regulatory Authority (MHRA) has approved Care Oncology Clinic’s request to report the results of the first retrospective study using data from patients already treated at the clinic. We completed an analysis of our 95 patient cohort with Glioblastoma Multiforme Grade IV (GBM IV – the most aggressive type of primary brain cancer).

The results are striking and show highly significant improvement in overall survival when compared to Public Health England (PHE) data for patients under 70 years old diagnosed with GBM IV between 2007-2013.

<table>
<thead>
<tr>
<th>Summary of preliminary results of the COC retrospective study</th>
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<tbody>
<tr>
<td>• Retrospective analysis of 95 patients with glioblastoma multiforme IV who attended the Care Oncology Clinic and were prescribed adjuvant COC Protocol alongside their usual care.</td>
</tr>
<tr>
<td>• Median survival for patients receiving the COC Protocol alongside maximal care (surgery + chemo-radiotherapy) was <strong>27.1 months</strong>, compared to just <strong>14.8 months</strong> for GBM patients in the PHE dataset.</td>
</tr>
<tr>
<td>• 2-year overall survival for patients receiving the COC Protocol alongside maximal care was 55.8%, more than double 2-year survival rate of 26.3% for GBM patients in the PHE dataset.</td>
</tr>
<tr>
<td>• The COC Protocol was well-tolerated by the majority of patients.</td>
</tr>
</tbody>
</table>

These data have been audited and confirmed by external biostatisticians, Cytel, in Geneva. Our results are now being compared against matched controls with a view to publication in a peer-reviewed journal in Q2 2018. For further information about these study results please contact the Care Oncology Clinic.

In addition to the positive evidence gathered by our own research programme, a wealth of published data also supports the individual use of the COC Protocol medications in cancer. This data is summarised in the following sections.
Published evidence of clinical safety

One of the main advantages to the repurposing of existing drugs is their well-established safety records. The literature contains well-defined profiles for pharmacokinetics, bioavailability, dosage, adverse-effects, toxicities, and interactions for each of the four drugs in the COC Protocol.

- **Metformin** was first licensed in France in 1957 and has since been prescribed to millions of patients worldwide to control hyperglycaemia. It has a very well-established safety profile\(^\text{74}\). Gastrointestinal adverse effects (in particular on initiation of therapy) are quite common, and most often mild and manageable\(^\text{75,76}\).

- **Atorvastatin** a lipophilic statin, has been clinically available and widely prescribed to regulate high cholesterol since the 1990s. Most people tolerate statins well without any problems\(^\text{77}\). Muscle and joint pain complaints are a relatively common adverse effect, which can usually be well managed\(^\text{78}\). Statins were well tolerated by cancer patients in early-phase clinical trials carried out in the 1990s\(^\text{79,80}\).

- **Doxycycline** a tetracycline antibiotic has been used clinically for more than four decades. Common adverse-effects include gastrointestinal problems and photosensitivity\(^\text{81}\). Owing to the regular use of doxycycline for dermatological conditions such as acne, long-term effects of this drug are well documented\(^\text{82}\).

- **Mebendazole** is commonly used to treat parasitic worm infections. It has low-toxicity, even at higher prolonged doses, and generally minor adverse-effects\(^\text{83}\).

Furthermore, the Care Oncology Clinic has been treating patients in the UK with the COC Protocol since 2013. We have now seen over 1450 patients, and logged thousands of patient hours of experience with their treatment. The full COC Protocol builds on this experience, and our prescribing clinicians are skilled in the use of the COC Protocol medications in cancer. They have specialist knowledge of dosage optimisation and frequency, titration modulation strategies, potential adverse effects of the medicines when used in cancer, and possible interactions to watch for when the patient is undergoing other standard treatments (such as chemotherapy, radiotherapy, hormone therapy, and immunotherapy). This specialist knowledge is essential for the care of patients taking COC Protocol medications off-label. Each medication is used within the established, standard dosing ranges for their labelled indications, and our clinicians seek to further optimise and maintain patients on doses that are both therapeutic and well-tolerated.

Published evidence of clinical efficacy

There is a significant amount of preclinical, retrospective and observational evidence supporting the anticancer activity of each of the individual components of the COC Protocol. Some prospective clinical data are now also emerging, and more trials are underway, particularly for statins and metformin as individual or combined adjunctive therapies\(^\text{84}\).

Existing relevant clinical efficacy and safety data for the four constituents of the COC Protocol are briefly outlined below, and comprehensive reviews are referred to for further reading.
Metformin in cancer

Clinically, metformin is perhaps the most studied of the four COC Protocol drugs in the context of cancer. Numerous population studies in patients with type 2 diabetes have shown that metformin reduces the incidence of cancer (by as much as 30%)85, and cancer-related mortality, compared to those who do not take metformin and/or take other anti-diabetic medications86,87,88,89,90.

Retrospective and observational studies in diabetic cancer populations have consistently associated metformin use with better survival outcomes for a number of cancers, including kidney cancer91, liver cancer92, endometrial cancer93, lung cancer94, colorectal cancer95, and in locally advanced, but not metastatic, pancreatic cancer96. Improved responses to standard cancer treatments are also supported by population studies. For example, a 2009 observational study showed that metformin use in diabetic breast cancer patients receiving neoadjuvant chemotherapy was associated with a pathologic complete response of 24%, compared to 8% in the non-metformin group, and 16% in the non-diabetic group97.

Prospective studies of metformin in cancer

Clinicaltrials.gov lists hundreds of ongoing clinical trials investigating metformin alone or in combination with traditional treatments for a number of different cancers98. Little survival data is yet available for these studies, however preliminary biomarker results from a number of prospective trials suggest favourable responses in metformin treated groups, particularly in early disease99.

For example, a small trial investigating the ‘window of opportunity’ for metformin in nondiabetic women with operable breast cancer found that short-term (18 days) pre-operative metformin ‘resulted in clinical and cellular changes consistent with beneficial anti-cancer effects’. Metformin was well tolerated in this group and adverse effects were mild100. Similar results were reported in studies investigating preoperative metformin (up to 4 weeks) in obese non-diabetic women with endometrial cancer101, and in another study of women with operable invasive breast cancer (more significant gastrointestinal issues were noted in this study)102.

In other studies; in colorectal cancer, low-dose metformin for one month suppressed the formation of rectal aberrant crypt foci in non-diabetic patients, suggesting metformin could help prevent colorectal cancer in patients at risk of the disease. No adverse-effects were reported103. In a time-to-relapse Phase 2 study, metformin when combined with standard-of-care, delayed relapse in endometrial cancer104. And in another Phase 2 study in castration-resistant metastatic prostate cancer, metformin showed promising effects on disease stabilisation105.

Metformin in pancreatic cancer

As more prospective data becomes available the exact benefits of metformin to cancer patients will become better established. For example, although systematic reviews of population cohort studies associate metformin use with improved survival in patients with pancreatic cancer, early results from two RCTs are less encouraging, with equivocal or seemingly worse survival in the group taking metformin106. Results from these trials suggest advanced pancreatic cancer patients may have difficulty tolerating metformin in certain treatment combinations, for example, with paclitaxel. This suggestion is supported by the meta-analysis
findings of Li et al (2017)\textsuperscript{107}, reported above. New clinical trials should focus on patients with earlier-stage disease and investigate using a different combination of agents\textsuperscript{108}.

**Statins in cancer**

There have been numerous clinical trials and epidemiology studies of statins and cancer.

Earlier epidemiological studies investigating the clinical effects of statins in cancer were somewhat inconsistent\textsuperscript{109}, perhaps in-part owing to the differential effects of lipophilic vs hydrophilic statins outlined above\textsuperscript{110,111}. However, more recent larger studies and meta-analyses consistently show reduced cancer incidence in statin users, and reduced cancer-related mortality in cancer patients who used statins\textsuperscript{112,113,114}.

A recent study by Wang et al (2016)\textsuperscript{115} examined data from the Women’s Health Initiative, a 15-year research program involving postmenopausal women aged 50 to 79 years who were enrolled between 1993 and 1998 at 40 centres in the US. The researchers found that, compared with never having used statins, current statin use was associated with a significant reduction in cancer mortality, with an adjusted hazard ratio (aHR) of 0.78 vs never use (P < .0001). Statin use was associated with significant reductions in deaths from breast (aHR = 0.60), ovarian (aHR = 0.58), colorectal (aHR = 0.57), digestive (aHR = 0.68), and bone/connective tissue cancers (aHR = 0.45), but not from lung cancer (aHR = 1.17). A follow-up article from the same group gives a useful in-depth discussion on the nature of this association and the challenges of adjusting for biased selection in population studies and calls for more well-designed prospective clinical studies to fully understand the potential benefit of statins in cancer\textsuperscript{116}.

There are a number of relatively small early-stage clinical trials outlining the benefits of statins in the treatment and adjuvant treatment of cancer, stretching back to the 1990s. These trials are discussed thoroughly in Chan et al, (2003)\textsuperscript{117}, Hindler et al (2006)\textsuperscript{118}, and Chae et al (2015)\textsuperscript{119}. These studies have reported promising results with statins in a number of cancers, including paediatric brain tumours, early stage breast cancer, liver cancer, colorectal cancer, and myeloma and leukaemia. For example, in a 2001 randomised trial involving 91 patients with advanced liver cancer, median survival was 18 months in the pravastatin/5-fluorouracil group, compared to 9 months in the control group (p<0.006)\textsuperscript{120}. In all of these trials statin use was well tolerated.

However, some studies have reported mixed results\textsuperscript{121,122} and more evidence from larger studies is required to investigate exactly which patients will benefit from which statins.

**Potential therapeutic complementary activity of statins with metformin**

Some supportive clinical evidence also exists suggesting that the dual use of lipophilic statins and metformin can produce a complementary and potentially enhanced activity against cancer. Recent population-based studies have found enhanced effects on overall survival associated with statin and metformin combinatorial use in patients with gastrointestinal cancers\textsuperscript{123} and in patients with resectable pancreatic cancers\textsuperscript{124}. Other studies have also associated combined use of these medications with an enhanced protective effect against cancer in patients with Hepatitis B\textsuperscript{125}, with lower PSA levels in prostate cancer patients\textsuperscript{126}, and with modified risk of prostate cancer recurrence in diabetic patients after prostatectomy\textsuperscript{127}.

A 2015 study by Lu-Yao et al\textsuperscript{128} used Surveillance, Epidemiology and End Results–Medicare linked data to follow 22,110 patients diagnosed with high-risk prostate cancer. Patients who took both statins and metformin had a substantial reduction of 43% in prostate cancer-specific mortality, and this effect was more
pronounced in men with obesity/metabolic syndrome conditions. A similar pattern was also seen in patients who took statins alone, however patients who took metformin alone experienced no reduction in overall mortality compared with those who used neither medication. The authors concluded that potential benefits of metformin use may be secondary to concomitant statin use in this population.

**Mebendazole in cancer**

There are a number of preclinical and mechanistic studies supporting the potential anti-cancer activity of both mebendazole and doxycycline, and clinical results in humans in the context of cancer are now beginning to emerge.

Mebendazole activity in GBM was discovered serendipitously in 2011 by investigators, who observed that GBM xenografts were failing after mice models were fed albendazole to fight a spate of pin worm infections. Further investigation showed that both albendazole- and mebendazole-induced apoptosis in two GBM cells lines in vitro and in vivo.

At around the same time two case study reports, one concerning long-term tumour control in a patient with metastatic adrenocortical cancer, and one describing potential disease response to mebendazole in a patient with metastatic colon cancer, were reported in the literature, and are discussed below. These case studies, along with a summary of two ongoing clinical trials in the US for mebendazole in cancer are discussed in detail in Pantziarka et al (2014).

**Case Study 1: mebendazole in metastatic adrenocortical cancer**

In 2011, a case of long-term tumour control in metastatic adrenocortical cancer was published. The patient had experienced disease progression despite multiple chemotherapeutic protocols and several rounds of surgery. After all other treatment options had been exhausted, the patient discovered the preclinical evidence of mebendazole action against adrenocortical cancer via Pubmed and forwarded the information to the clinicians, who agreed to use it based on this evidence and the relatively low toxicity of treatment.

Mebendazole monotherapy at 100 mg twice a day was commenced. The patient experienced some regression in metastatic lesions, and overall the disease remained stable for 19 months, tolerating the treatment without adverse effects. Quality of life returned to his baseline prior to his initial surgery. However, 24 months after the commencement of oral mebendazole a scan showed disease progression, and everolimus was added to the mebendazole but without additional benefit in disease control.

**Case Study 2: mebendazole in metastatic colon cancer**

A case of metastatic colon cancer treated with mebendazole was described in 2014. Here, a 74-year-old patient suffering from progressive metastatic colon cancer who had no standard treatment options left was started on 100 mg mebendazole twice a day. Mebendazole was selected based on the author’s previous preclinical work with the drug.

After six weeks of monotherapy, radiological evaluation showed near complete remission of metastatic lesions in the lungs and lymph nodes and a good partial remission in the liver. However, the patient experienced elevated liver enzymes, so mebendazole was temporarily stopped and then started at half the
dose, with the patient reporting no ill effects. Liver enzymes normalised and a subsequent round of CT scans confirmed the initial disease response. After ceasing treatment for approximately three months, the patient developed brain metastases that were treated with radiotherapy, following by evidence of disease in the lymph nodes. Mebendazole treatment was not recommenced following the discovery of the brain metastases or in subsequent disease progression.

**Doxycycline in cancer**

Tetracyclines like doxycycline have much therapeutic potential in cancer due to their reported anti-microbial, anti-inflammatory, and immune-modulating effects\(^{134}\). For example, the antibacterial properties of doxycycline are known to be of use in the treatment of *Chlamydia psittaci* related ocular adnexal MALT lymphoma. In one multi-centre prospective trial in Italy, doxycycline was found to be a ‘fast, safe, and active’ therapy for this cancerous condition\(^{135}\).

However, little benefit was found by combining doxycycline with targeted therapies in two small studies for advanced renal cell carcinoma and advanced breast cancer\(^{136,137}\). The results of further clinical studies investigating doxycycline in cancer, and in particular doxycycline in combination with metformin in cancer, are eagerly awaited\(^{138,139}\).
The METRICSplus research programme

METRICSplus has been planned with help from Dr Sarah Edwards at the University College London, a key opinion leader in the health research ethics field. The aim of this research programme is to monitor and ensure that Care Oncology Clinic’s pioneering real-world evidence strategy is as near equivalent as possible in social value to classically designed Phase 3 clinical studies.

Briefly, the METRICSplus research strategy includes:

- **METRICS**: a large-scale prospective interventional study in a real-world clinical setting investigating survival and biomarker outcomes in patients with cancer attending the Care Oncology Clinic and who are prescribed the COC Protocol. The MHRA has approved this new study of the work of the Care Oncology Clinic as an Intervventional Service Evaluation, and ethical approval was received from the designated Research Ethics Committee in July 2017. This study will commence formal enrolment in 2018.

- **Kings sub-study and Barts sub-study**: two supporting mechanistic imaging studies in smaller subsets of patients (20 patients and 10 patients respectively). These studies will investigate biomarker and tumour metabolic marker changes during treatment with the COC Protocol. These studies will be carried out with the help of King’s College Hospital London (Dept. of Neuro-Imaging Sciences) and St. Bartholomew’s Hospital London (Dept. of Nuclear Medicine).

- **One Health study**: A further additional study based on outcomes of real-world veterinary patients prescribed the COC Protocol is planned. The clinical similarity of some cancer types in both animals and humans is increasingly being recognised and the use of real-world evidence derived from a veterinary setting is becoming increasingly important.

- **UCL PhD Project**: Care Oncology Clinic will fund a PhD student under the supervision of Dr Sarah Edwards. The aim of this research will be to evaluate and help ensure that Care Oncology Clinic’s pioneering evidence strategy is as near equivalent as possible in social value to classically designed Phase 3 clinical studies.

For more information about Care Oncology Clinic’s research strategy please contact us directly or visit the website at [www.CareOncologyClinic.com](http://www.CareOncologyClinic.com).
The Care Oncology Clinic: the service we provide to patients

Patients who attend the Care Oncology Clinic will receive the following services:

a. An initial consultation with one of our oncologists or physicians, during which the patient’s medical records will be reviewed in full, and a full case history will be taken. Our physicians will need to learn all about the patient and their current health, as well as all the treatments that have been received or are planned. The COC Protocol will be discussed in detail, and the risks of taking drugs on an “off-label” basis will be explained. COC only prescribes medications within the safe, recommended dosing limits and dosing schedules for each drug’s on-label indications. Combinations and doses are tailored to a) the type of disease being treated and b) each individual patient’s health status. COC reviews concomitant medication, baseline medical information and blood levels and organ function, prior to prescribing and checks these again at regular intervals.

b. If the patient wishes to proceed with the treatment, then a prescription will be given – normally for 3 months.

c. Following the appointment, the clinical team are available to answer any questions about the treatment, and to assist the patient if they encounter any side-effects. Care Oncology Clinic can usually make adjustments to the treatment to reduce any unexpected side-effects and can advise about interactions with other cancer treatments at any time.

d. Care Oncology Clinic provides ongoing support to all patients and has an out-of-hours telephone service from which the patient can receive a call-back if needed.

e. Every three months, the patient will be asked to return to the clinic, and to provide updated medical records from their primary care-providers (i.e. in the UK, this will be the NHS). The physician and the patient will discuss progress, the patient’s health as well as the treatments being provided by the NHS (or other provider) at that point. The prescription can then be adjusted or renewed.

f. In the event that the patient is ill and does not wish to travel to the clinic for an appointment, then it is possible for the consultation to be carried out remotely via teleconferencing.

g. Care Oncology Clinic collects all medical data from patients and with the patient’s consent, the medical data is anonymised and aggregated for analysis of outcomes. This allows the clinic to study the efficacy and safety of the treatment in different cancers.

h. Care Oncology Clinic is also working on improving the medicines themselves – with the aim of reformulating them to make them more effective in cancer treatment at lower doses, i.e. reducing the likelihood of side-effects, without compromising efficacy.
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