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Review Article

Novel Immunoendocrine Therapy of Advanced Cancers of all types Opens a New Medical Field for Clinical and Research Endocrinologists

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Abstract

Main Objective: To show evidence that the best treatment option for advanced metastatic cancer of all types is the use of progesterone receptor (PR) modulators e.g., mifepristone, to inhibit the production of immunomodulatory proteins e.g., the progesterone induced blocking factor (PIBF) or the progesterone receptor membrane component-1 (PGRMC-1) by membrane (m) PRs which allow tumor invasion of normal tissue, and even more importantly, allow the cancer to evade immune surveillance despite the presence of foreign antigens.

Methods: Patients with advanced cancers without other medical options that were devoid of the classical nuclear (n) PR were treated orally with 200mg per day oral mifepristone and a minority received 300mg /day. They were monitored by quality of life and length of life.

Results: Evidence of considerate palliative relief and extension of life (sometimes over 5 years) were seen with over 12 different types of cancer and in all patients except some who were within one week of death. Palliative benefits were seen shortly after starting therapy even without evidence of tumor regression. Metastatic spread was markedly thwarted. A few showed complete tumor regression.

Conclusion: Since this therapy is considered to be outpatient therapy, and can be given as a simple oral pill, the best group to prescribe this immunoendocrine therapy with mPR antoginists would be medical endocrinologists especially considering that with certain drug interactions, the drug could block the glucocorticoid receptor leading to symptoms of adrenal insufficiency and hypokalemia.

Keywords: Metastatic cancer, Membrane progesterone receptors, Immuno-modulatory proteins, Selective progesterone receptor modulators

Introduction

At present, the field of medical endocrinology is one of the least sought-after specialties of internal medicine. Actually because of so many diabetics, there is probably a shortage of endocrinologists, but most cases of diabetes are treated by family physicians and in ternal medicine specialists leaving the most difficult cases to the endocrinologists. Although insulin is a hormone that technically classifies diabetes mellitus as an endocrine disorder, because of its damaging effects on various other systems of the body e.g., kidney,

heart, and brain, where complications may involve hospitalization for the various complications, one could argue that the condition should be managed more by generalists in internal medicine or other subspecialities e.g., renal, cardiac, or neurology depending on where there may be other associated medical complications.

Many clinical endocrinologists prefer an outpatient type of practice, but the frequent complications requiring hospitalization for diabetes mellitus encourages some endocrinologists to eliminate diabetes mellitus from their practice, or purposely go into strictly academics, or research, or pharmaceuticals. However, for those physicians who are enamored with the science of endocrinology, but want to limit their practice to endocrine disorders, but not diabetes, they will frequently not have a sufficient number of patients to achieve competitive financial compensations compared to other subspecialists.

Part of the problem is that most common non-diabetic endocrine problems e.g., hypothyroidism can be easily treated by family physicians or internal medical specialists. Graves' disease may be referred to internal medicine rather than to an endocrinologist for anti-thyroid drugs or nuclear medicine for radioactive iodine. Adrenal disorders are very rare as are growth hormone excess or deficiency. Hirsutism is generally managed by reproductive endocrinologists, impotence by urologists, thyroid nodules by surgeons, etc. Thus, there are few conditions that lead to frequent return visits for long-term management of endocrine disorders by endocrinologists if one is not also a diabetologist.

The objective of this perspective is to introduce a common disorder that would markedly increase the patient volume for the medical endocrinologist that can be performed in an outpatient setting that will prove very satisfying to the endocrinologists, because there are preliminary data that immuno-endocrine therapy will not only significantly extend life of patients with advanced cancer but will help the patients to markedly improve the quality of their lives. Even more importantly, there would be little competition for these patients from other medical specialties.

In this manuscript, the author will provide the background research supporting this immuno-endocrine therapy for advanced cancer, by providing strong anecdotal evidence of the beneficial therapeutic effect of this therapy leading to possibly years of happy outpatient appointments for the medical endocrinologists in contrast to the bleak prognosis for therapy provided by oncologists. Fortunately, based on anecdotal experience, the author will provide his view as to why this condition, i.e., advanced treatment-resistant end-stage cancer will not be usurped by oncologists. Finally, these new concepts will hopefully help those endocrinologists more interested in research or the pharmacologic industry to focus more on immuno-endocrine therapy to develop even more efficacious treatments compared to what is presently available.

Background

Based on the similarity of the fetal-placental unit and cancer, i.e., Rapid Proliferation of cells, invasion of normal tissue, and evasion of immune surveillance, it was hypothesized that it was likely that the malignant tumor would utilize a mechanism that was already in place for survival of the fetus [1]. Though far less immunogenic than the fetal semi-allograft, it was reasonable to consider that the foreign antigens present in most or all malignant tumors would require a way to silence cellular immune rejection of the cancer. The author, for sake of brevity, will briefly summarize the hypothetical model leading to successful immuno-endocrine therapy of advanced cancer. However, for those interested in the research leading to this hypothetical model there are several other summary articles that one could read [2-9].

The simplified theory suggests that in order to proliferate and survive, all, or most cancers, must activate Membrane Progesterone Receptors (mPRs) to produce Certain Immunomodulatory Proteins e.g., the Progesterone Induced Blocking Factor (PIBF) or the Progesterone Receptor Membrane Component-1(PGRMC-1) proteins, and these immunomodulatory proteins help the tumor to invade normal tissue and evade immune surveillance [4,10-12].

Over 30 years ago, based on the demonstration of clinical benefit to blocking the Estrogen Receptor (ER) in cancers that were positive for the nuclear ER with Selective Estrogen Receptor Modulators (SERMs), that perhaps blocking the nPR with a Selective PR Modulator (SPRM) could also prove beneficial to patients with cancers wtih the nPR present. However, early studies with nPR positive breast and ovarian cancer treated with PR modulators e.g., mifepristone, were disappointing [13-15]. It is well known that the presence of the nPR in cancer is associated with a better prognosis. Thus, the lukewarm response to thwart tumor progression in patients with nPR positive cancers following mifepristone therapy could be explained by the theory that, whereas mifepristone may block cancer progression by inhibiting activation of the mPR (thus inhibiting production of immunomodulatory protein e.g., PIBF), it is also suppressing protective factors produced by inhibiting nPRs [16]. Thus, possibly PR antagonists would be more suited for cancers devoid of the nPR. Nevertheless, when cancers that are positive for the nPR metastasize, generally they will have lost the protective nPR and may now respond to PR antagonists e.g., mifepristone [17].

Anecdotal Human Experience Supports the Provocative Statement that the Use of PR Antagonist/Modulators for the Treatment of Advanced Metastatic Cancer is Best Suited for Endocrinologists to Render Treatment Rather than Oncologists

There are no controlled studies or large series in treating humans with advanced cancers with PR antagonists especially those known to be nPR negative. However, there are placebo-controlled studies in mice with spontaneous leukemia/lymphoma, lung, prostate, and testicular cancer showing significant extension of life and improvement of quality of life (as evidenced by body conditioning scores) with oral mifepristone therapy [18-20].

There have been, however, case reports showing marked extension of life and improvement in quality of life in the large majority of cases of advanced metastatic cancer in humans with no more

treatment options available which leaves little doubt about the efficacy of mifepristone therapy for end stage cancers. The recounting of these case reports will add new information not found in the published cases supporting the contention that for various reasons, clinical oncologists, even when made aware of the efficacy of this treatment, will still advise hospice, or now suggest some other therapies that they did not suggest until the use of mifepristone was brought to their attention. The hope of this author is that these case reports will convince many endocrinologists to try mifepristone in a large group of patients with advanced cancer and that they will share a similar experience with the author, and thus begin treating end stage cancers with PR modulators/antagonist. This could possibly become a staple type of patients treated by medical endocrinologists. Mifepristone may be the best pharmacologic agent available in the pharmacologic market to treat advanced cancer [21]. If these anecdotal cases are supported by the experience of a large number of medical endocrinologists, not only would this provide a large new group of patients to keep clinical endocrinologists busy for years, but provide a new concept for scientists in endocrinology to explore and hopefully develop even more efficacious immuno-endocrine drugs that will inhibit the mPRs of these cancers from making immunomodulatory proteins that enable cancer to evade immune surveillance.

Adenocarcinoma of the Colon [22]

Our first published human case with extensive end-stage cancer that we treated with oral 200 mg mifepristone was a 61-year-old woman whose primary adenocarcinoma of the transverse colon was resected. However, when subsequently the cancer had extensively metastasized to the liver, peritoneum, ovaries, and uterus associated with marked ascites, they told her she would probably live no more than one month, and that chemotherapy would probably not improve her lifespan very much.

She was aware of our cancer cell line studies and animal research and asked if we would be willing to treat her with mifepristone. At that time a physician could not use the mifepristone off-label unless a compassionate use IND was granted by the FDA. When we received approval, she started single agent oral mifepristone 200mg/day.

Five weeks from starting mifepristone, she stated that she was feeling very well with no pain and good energy. Her ascites had disappeared. A CT scan showed no increase in either number or size of any of the lesions. Though initially her oncologist denied her to have treatment with chemotherapy, seeing more clinical improvement and stable disease, and a marked decrease in her carcinoembryonic antigen (CEA) level to 1.9 ng/ml, they decided to add chemotherapy with bevacizumab and 5 fluorouracil. Though she had mild side effects with these chemotherapy drugs (she had none with mifepristone), she was willing to stay on all three medications to hope for a cure.

After one and a half years on mifepristone, she was conducting a perfectly normal life with no restrictions of any activities, and there had not been any growth of any of the metastatic lesions and no recurrence of the primary 6.5 cm lesion that had been surgically excised. Her CEA was 1.3 ng/ml. Her chemotherapy was paid for by her insurance, but not the mifepristone which cost her over $500 dollars per month. She asked the oncologist if they thought she could reduce the dosage of mifepristone to 200 mg every other day. They thought that should be sufficient especially since she is also taking chemotherapy [22].

Neither the patient nor the oncologist asked for the author's opinion. At 21 months on mifepristone (but three months on a 50% reduced dosage of mifepristone), the lesions started to grow for the first time. However, she was still feeling quite well with no pain and good energy. Nevertheless, the oncologist told her to stop the chemotherapy and the mifepristone.

Only at this point did she re-consult us to get our opinion if she should stop the mifepristone also. We advised her to stay on it, but we were unaware that she cut the dosage in half. She was still pain free and had good energy until 27 months when ascites returned. She only had mild abdominal discomfort from the ascites but was still ambulatory and carrying out daily function until her death after 30 months of taking mifepristone.

We only found out a few years later from her sister that she reduced the dosage of mifepristone. Furthermore, this case helps the author's contention that treatment of end stage cancer should be directed by medical endocrinologists and not oncologists [22].

There were several lessons learned from this case 1) The PR antagonist mifepristone can seem to thwart cancer progression in a human cancer not known to be positive for the nPR. 2) Colon cancer seems to be one cancer where mifepristone inhibits further spread. 3) Even though none of the metastatic lesions decreased in size, or disappeared following mifepristone therapy within the first month, she felt so much better. For the month prior to her surgery, she was in a lot of pain and had no energy. She felt worse after surgery. However, within a month of taking mifepristone, she felt like a new person despite no decrease in number or size of metastatic lesions. Even when she cut the dosage of mifepristone in half, which probably was responsible for allowing growth again of metastatic lesions, she continued without pain and good energy and mental clarity. In fact, the mild side effects from bevacizumab and 5-fluorouracil disappeared when she stopped those medications. Thus, despite the metastatic lesions growing, she actually felt better. 4) Mifepristone can be used in conjunction with bevacizumab or 5 fluorouracil. 5) One should not use less than 200 mg/ day of mifepristone.

This case supports treatment by endocrinologists rather than oncologists as follows. 1) The oncologists initially told her that she was too advanced for chemotherapy, but when she was doing well on mifepristone, they decided to now treat her with chemotherapy. Perhaps they were now hoping for "the cure." However, it is very clear today that once cancer has extensively metastasized, except in some rare instances, a cure is not possible. Thus, a medical endocrinologist would be satisfied with the good quality of life and extension of life span without feeling the need to add chemotherapy drugs that will not increase her lifespan, but negatively affect the

quality of life because of side effects. 2) The oncologists, without any knowledge of PR modulators to treat cancer, never contacted our group to inquire about the drug she was taking that seemed to stop metastatic spread. Even more importantly, mifepristone markedly improved her quality of life. This was the author's first experience of many where the clinical oncologists only seemed to be interested in "standard" treatments or to be involved in lucrative clinical trials. Certainly, the oncologists had the right to stop the chemotherapy, but showed complete disinterest and lack of respect for other treating physicians when they advised her to stop the mifepristone without at least inquiring our opinion or advise the woman to call our office to get an opinion. She called the author on her own who only wishes that she had told him that she had reduced the dosage of mifepristone. Nevertheless, even though the lesions were growing, she still had one good additional quality year left to be with her family and friends where she was completely functional without pain, and thus free of taking opiates, or for that matter, any analgesics.

A second case from that same publication was reported on an 83-year-old man who had colon cancer which metastasized to his lungs, liver, peritoneum, chest wall, and lymph nodes [22]. Despite capecitabine and cetuximab the lesions rapidly progressed. Though he was not in a lot of pain, he was too weak to get out of bed. He did have pain in his fingertips of both hands which started soon after chemotherapy with cetuximab. After two weeks of mifepristone, he was feeling so good that he went out for dinners and enjoyed other activities with marked improvement in energy and no longer side effects from the two chemotherapy drugs. An MRI four and a half months later found no new lesions or growths of any pre-existing metastatic lesions. Unfortunately, he died from an acute myocardial infarction! Though in the second case we cannot state for sure that had he not had a myocardial infraction he would have definitely lived longer (he also had azotemia), but for sure the drug improved his quality of life.

This second case helps support the author's contention that endocrinologists are best suited to treat advanced cancer with mifepristone. Whereas the endocrinologist would be quite satisfied with his improvement in quality of life, the oncologist would have stopped the drug because of its failure to induce remission of the malignant lesions. Clinical oncologists get excited to see lesions shrink or even disappear, even if the cancer eventually finds a way to develop resistance to the drug. Possibly the patient's life may be only extended by a few months by chemotherapy but compromised by side effects of these anti-cancer drugs, hospital admissions, etc., all taking a toll on quality of life.

Thymic Epithelial Cell Cancer [23]

Thymic epithelial cell cancer (not a thymoma) is a rare cancer. One patient who we were treating for gynecologic problems was diagnosed with thymic epithelial cancer at age 46. She had surgical excision followed by radiation therapy to the mediastinum and lung. Despite these treatments, the lung lesions continued to increase in size and number. She was symptomatic in that she complained of marked fatigue, dyspnea on exertion, and cough. There were no chemotherapy regimens at that time to treat this cancer, so she tried octreotide in a clinical trial. She stopped two months later because the octreotide did not thwart progression at all. She was very symptomatic at this time with marked fatigue and marked dyspnea on exertion. However, she would not quite be considered moribund or end stage cancer at this time. Nevertheless, the FDA approved a compassionate use IND for mifepristone.

Though the aforementioned patient with colon cancer was our first moribund patient with cancer that we treated, this 46-year-old woman was the first patient that we ever treated with mifepristone. During two years of single agent mifepristone therapy, she had marked improvement in her energy and shortness of breath and decrease in cough. Interestingly, the improved symptomatology occurred despite no shrinkage of any of the lesions. However, over two years there was very little growth of pre-existing lesions and no new ones appeared [23].

Lessons learned from this case. 1) it seems that typical symptoms of progressive cancer seem to be more related to a factor produced by the cancer cells that also allows their proliferation rather than mechanical space occupying effects 2) Patients feel better soon after starting mifepristone, even before there is apparent decrease in tumor burden. Mifepristone not only provides immediate palliative benefits, but also increases length of life. According to the Thymic Epithelial Cell Carcinoma Society at that time, she had the second longest lifespan with this very aggressive tumor than any other previous patient with this type of cancer, and she would have been the longest if the radiation therapy physician had not intervened as seen below.

This case also supports the contention that endocrinologists would be best suited to treat most cancers with PR antagonists that do not have any other treatment options. Her main oncologist was now her radiation therapy physician. He decided without consulting us to provide a second course of radiation therapy at the two-year mark. He also suggested to stop the mifepristone therapy to see if there was any benefit to the radiation treatment, but to resume mifepristone if the second course of radiation did not eradicate the lesions. It is not clear what was his thought process as to why a second course of radiation therapy to a field that has already been irradiated will have some positive benefits for the patient with that cancer when the first course of radiation therapy provided no benefits at all!

As a complication of the second course of radiation therapy, she developed severe pulmonary fibrosis which placed her in a moribund state. Since mifepristone was not going to reverse the pulmonary fibrosis, it was not resumed. She died two months after her second course of radiation therapy. Interestingly, without mifepristone, there was resumption of rapid growth of pre-existing metastatic lesions and even new ones despite the second course of radiation therapy [23].

These events clearly show that the decision made by the oncologist was a poor one, and not only because of causing a lethal complication, but by telling the patient to stop mifepristone thus allow-

ing rapid spread before mifepristone could be initiated again. The reduced dosage of mifepristone in the aforementioned case of colon cancer may have at least prevented very rapid progression. But this case of thymic epithelial cell cancer may have taught the lesson to strongly advise the patient that once you start taking the drug, do not stop. This case suggests that by blocking certain factors that involve the PR (possibly PIBF), the cancer will at least arrest further growth and metastasis, but not "cure" cancer once it metastasizes. Either the product made by the mPR contributes to the asthenia of cancer, or possibly the spread of cancer itself, but by blocking the membrane PR and its products seems to make the patient feel a lot better, not just for a short time, but years instead of weeks or months. It seems that, in contrast to chemotherapy or immunotherapy, the cancer does not seem to mutate to PR antagonists thus preventing resistance to mifepristone. This allows long-term palliative benefit and extension of life following PR antagonist therapy. This is a concept more likely to be understood by endocrinologists rather than oncologists who would be more apt to stop treatment, as demonstrated even if the patient feels a lot better, if there is no obvious tumor regression. Even worse, the oncologist may decide to try a different anti-cancer drug or other therapy not likely to be effective because the clinical oncologists sadly may be influenced by the financial benefits to the oncology department of a specific therapy, e.g., radiation treatment, or may be more apt to stop a drug that is providing marked clinical benefit, but not totally eradicating lesions, to influence them to try a pharmaceutical company clinical trial of a new anti-cancer drug that may theoretically "cure" the cancer. The medical endocrinologist would be less likely than oncologists to opt for other therapies or clinical trials that would be more profitable because the pharmaceutical companies would be looking to oncology departments with available facilities to handle complications of the drug or have the facilities to evaluate disease progression needed for the drug company to gain FDA approval. Except for research purposes, the exclusive dispensing of an oral pill for end-stage patients with cancer who have no other treatment options allows merely outpatient office visits without hospitalization related to complications of chemo or immuno-therapy drugs or the need for invasive monitoring for disease progression. This would save the health industry billions of dollars.

Transitional Cell Carcinoma of the Renal Pelvis [23]

Another very moribund patient that we treated with mifepristone was a 73-year-old male with extremely aggressive transitional cell carcinoma of the renal pelvis. The family was advised that he only had a week to live despite radical surgery and two different courses of chemotherapy. We obtained a compassionate use IND approval by the FDA. He was semi-comatose at the time of treatment, partly from marked asthenia from the cancer, and partly from high dosage opiates he was taking which only minimally reduced his pain.

He died two months later and initially we considered this case a failure with mifepristone. We thought the oncologist could not know for sure that he only had one week to live. Subsequently, from talking to his wife, and then about three months after his death, his oncologist called the author, and after these conversations, this case does represent evidence of significant palliative benefits of mifepristone for a different type of cancer, i.e. traditional cell carcinoma of the renal pelvis [23].

After his death his wife called to thank us for giving her another two great months with her husband. Within a few days, his energy markedly improved, he hardly any pain at all, and without the aid of the opioids, merely using acetaminophen on occasion. His mental status returned to normal. She was so appreciative that for years she paid for the mifepristone for other patients who could not afford it. At that time with a 50% reduction in price which was given when one obtained a compassionate use IND, the price was twenty-one dollars a pill.

The conversation with the oncologist was just as interesting. They assumed that he only had a week to live because the tumor was wrapped around some major arteries, and it was just a matter of time before one ruptured and he would bleed to death. The oncologist was from a world-renowned medical center that is known for treating unusual cases. The oncologist stated that they have never witnessed a tumor that metastasized as rapidly as this cancer. Every three months, his CT scan would find an "explosion of new metastases." When he was still alive after six weeks of mifepristone they decided to repeat his CT scan. They found for the first time no new metastases, and, in fact, some were getting smaller.

Lesson to be learned from this case:1) Even with death appearing imminent, there still may be benefit to treatment with mifepristone. 2) Once again, the patient noted that he felt much better with basically the same number of lesions, once the mechanism to allow continual spread was stopped. 3) This was now the third different type of cancer that had no other treatment options which responded to mifepristone. None of these tumors were known to be positive for the nPR. Assuming the main target for mifepristone benefit is suppression of PIBF, could this immunomodulatory protein be the one universal protein that all tumors need to proliferate? Is it possible that mifepristone or other PR antagonists will prove to be the only anti-cancer treatment that can have anti-cancer benefit for all cancers (4)?

This case also supports the contention that this drug should be used primarily by endocrinologists rather than oncologists. Oncologists do not seem to be interested in drugs that provide palliation rather than cure. If this concept spread amongst the endocrinologists, and became a staple of treatment, they could, as a group, not only negotiate with the pharmaceutical company to reduce the price for patients with cancer but may convince insurance companies to pay for the drug in lieu of much more expensive anti-cancer drugs. Though we were pleasantly surprised by the phone call from the oncologist, he only expressed his interest in participating in a clinical trial if some pharmaceutical company was sponsoring such a trial.

Probable Small Cell Lung Cancer [24, 25]

A moribund 80-year-old woman with advanced lung cancer is probably the case that best illustrates the benefit of mifepristone

for advanced cancers, and why the drug should be in the hands of endocrinologists. An 80-year-old woman developed sudden severe dyspnea on exertion and marked weakness. The chest x-ray and CT scan showed multiple lung lesions and bilateral pleural effusion with a po2 of 72 mm Hg and serum sodium of 118 m. She refused a lung biopsy since the results would not change the management. The oncologist concluded that based on the rapidity of symptoms, and presentation on first evaluation with extensive metastatic lung disease, and with the syndrome of inappropriate anti-diuretic hormone, she most likely had small cell lung cancer. The oncologist estimated that death would be within two weeks. She was advised to consult hospice.

The patient was actually the author's mother-in-law. He convinced her to try mifepristone. In the first month, she was feeling much better with much improved energy and no shortness of breath. After one month of single agent mifepristone therapy, her PO2 was now 99mm Hg and her serum sodium was 145 mmo/1L [24,25].

She was the first case to demonstrate complete regression of all of her lung lesions, though the chest x-ray still showed a ground glass appearance. Her probable small cell lung cancer never returned while she continued 200mg daily oral mifepristone daily. She died five years later at the age of 85 with a myocardial infraction [25].

Lesson to be learned: Even when imminent death seems certain, it is worth it to try mifepristone. Support for the contention that the use of mifepristone is best suited for endocrinologist's vs oncologists: Once there are no standard or clinical trial options, oncologists want to move on to treat the large number of patients who need their clinical expertise in prescribing standard anti-cancer medications. When they can no longer help the patient with present day therapy, then they appropriately refer them to a new group of physicians, e.g., palliative care/hospice physicians who can minimize their suffering until relieved by death. With their busy schedules, oncologists generally no longer tend to that patient anymore. Case in point.

Before this woman developed lung cancer, she had been under the care of a hematologist/oncologist for chronic lymphocytic leukemia. Her treatment at that time was just observation. He was the physician who saw her in the hospital with probable SCLC. He never inquired about her outcome. When she was doing so well, after one year of single agent mifepristone, the author wrote him a letter explaining how well she was doing and sent him some publications about our treatment of cancer with mifepristone. He never responded. When the lead author was invited recently to write an article for a medical endocrine journal, he wrote about the endocrine paraneoplastic syndrome and mentioned the unique use of mifepristone to treat it using this case as an example [25]. Once again, the oncologist sent the publication, but he never responded. In contrast most endocrinologists would be fascinated by this case. For some reason practicing clinical oncologists do not seem to be interested in learning about a new, extremely safe, very tolerable treatment for cancer that, though off label, is available for immediate treatment of their cancer patients. In the author's experience the large majority of oncologists who observe their patients doing well on mifepristone have never called to inquire about the treatment. Thus, more support for the contention that mifepristone treatment should be rendered by endocrinologists observing these patients who are near death doing so well with an oral PR modulator. Adoption of this therapy could markedly increase patient volume for those endocrinologists who need more patients to make a decent living. Since the patient must obtain the drug at the physician's office, they would be seen monthly, and the visits could easily be shared with a nurse or nurse practitioner. Incidentally, during the 5 years of treatment her chronic lymphocytic leukemia did not advance either.

End Stage Pancreatic Cancer [26]

A 57-year-old man with end-stage pancreatic cancer was admitted to home hospice. He was started on opioids to reduce his severe pain. After one week of hospice, his sons heard from a friend about mifepristone. Upon his first visit, he was slumped over in a wheelchair, and he could barely talk.

Nevertheless, he understood the possible benefits of mifepristone and he was able to start five days later. They did not have sufficient funds to purchase the usual three-month supply. Since his case did receive a compassionate use IND from the FDA, there would be a 50% reduction in price, and they would need to pay about $1800 for three months. However, if he would die in two weeks, they would have wasted that money, which would have been a hardship for them. The author agreed to purchase the three-month supply and have them purchase just two weeks at a time. If he was alive and doing well for two weeks, they will purchase another two weeks, etc.

When he returned in two weeks, he came into the office walking with a walker. He stated he had marked reduction in pain and a considerable improvement in his energy. The next two weeks, he came in with a cane and was still feeling good. After one month of treatment, he was no longer taking any analgesics and walking without any assistance.

He continued to do very well for nine months on single agent mifepristone. He wanted to go back to work, but his job had been replaced, and he was unable to find another job. His children were paying for the drug. He decided that it was too much of a financial burden for his children, so he stopped the mifepristone. He died two weeks later.

Lesson to be learned: This case exemplifies that PR antagonist therapy is not a cure, but a way to provide significant palliation while able to maintain a normal meaningful life with full cognition. There is no question about the benefits provided by a palliative care/hospice team. However, it is obvious that even better than abrogating pain awaiting the final relief of death, would be to not only provide marked relief of pain, but to allow a resumption of normal activities, and spend more quality time with loved ones, and thus maintain a normal human existence.

We treated another case of advanced pancreatic cancer [23]. A 58-year-old woman with stage 4 pancreatic cancer widely metastatic to her liver failed to show any response to chemotherapy. Despite palliative care, she was still in a great deal of pain [23].

Her husband, a physician, heard about the treatment with mifepristone. Within two weeks of taking mifepristone, her husband stated that her degree of pain markedly improved so that her requirement for narcotics dropped to less than a third of what it was before starting mifepristone. Her energy had also markedly improved. After one month, she hardly had any pain.

However, her oncologist called with great news. She was approved for an early phase study of a new chemotherapy drug. She would be one of the first patients given this new clinical trial drug. Her husband, without seeking our opinion, agreed to begin this new clinical trial. Within two days, this drug proved to be cardiotoxic and caused marked damage to her heart. She was not eligible for a heart transplant, so she died in heart failure two weeks later. The drug was pulled from further testing because it became clear in humans that the drug was severely cardiotoxic.

Clinical trials, especially in the field of oncology, remunerate the oncology team extremely well. There is then a great temptation to convince patients who fulfill the eligibility criteria to register for these trials. It is highly unlikely that an endocrinologist would have advised this woman to stop a drug that was already showing significant clinical benefit in favor of an unknown drug with unknown efficacy and toxicity. Thus, it is the author's opinion that endocrinologists would be more suited for "immuno-endocrine" therapy of cancer because they would be less tempted to stop a drug that was clearly showing benefit for an unknown trial drug. Naturally, if a clinical trial for mifepristone was available or another PR antagonist/modulator which would be to the patient's best financial interest, advising such a trial would be appropriate. The continued publications finding significant clinical benefits from many different endocrine practices could prompt the pharmaceutical companies to attempt to re-purpose the drug which could lead to profitable clinical trials for medical endocrinologists.

Malignant Fibrous Histiocytoma [23]

A 23-year-old male presented with a widely metastasized malignant fibrous histiocytoma. He was advised that he only had two weeks to live. However, despite narcotics, he still suffered from intense pain. Within two weeks of taking single agent mifepristone his pain markedly improved, so that the pain was only mild and quite bearable. His opiate dosage was reduced to less than 25% of the dosage prior to mifepristone.

His energy returned and he resumed a functional life. After three and a half months of taking mifepristone, the pain started to intensify, and he died two weeks later. He did stay on the mifepristone until death. This was the first case where despite mifepristone providing definite palliative benefits and probably some extension of life, the cancer eventually spread rapidly and caused his death despite continuing the medication on a daily basis.

The patient stated that after one month of mifepristone that this was the best he felt since even before his cancer was diagnosed. None of his previous chemotherapy drugs improved cancer progression at all and he had tremendous side effects from all of them, yet had no adverse effects from mifepristone. He was advised by the oncologists that his prognosis was poor, and that chemotherapy would possibly only extend his life a few months. If the endocrinologists were known to provide oral mifepristone treatment for advanced cancer perhaps cases like the ones described may be referred from oncologists to endocrinologists rather than the hospice team.

Glioblastoma Multiforme Grade IV [27]

A 43-year-old male had end stage grade IV glioblastoma multiforme. He was advised that death was imminent. He was paralyzed from the neck down and his hands stayed in a clenched position. He was sleeping most of the day and he was not capable of normal conversation.

Within two weeks of taking mifepristone, he became much more alert and was able to converse normally. He was now able to use his hands but otherwise remained paralyzed. After three months of taking mifepristone, though his energy level remained good, and his mentation was still normal, he was still having some difficulty breathing and swallowing. He thanked us for the extra three months of life, stopped the mifepristone, went back to 100% hospice care and died two weeks later [27,28]. The most important new information that we learned from this case was that mifepristone can cross the blood-brain barrier.

Breast Cancer [17]

At age 31, this woman was diagnosed with stage III breast cancer with focal invasive ductal and lobular type that was positive for the ER and PR. Before starting chemotherapy, this young lady, who was not married, came for oocyte cryopreservation. Despite surgery, radiation therapy, tamoxifen, neoadjuvant chemotherapy and various other medications, including palbociclib, everlimas and fulvestrant, her cancer progressed locally and also metastasized distally to bone, liver, and bowel.

At the age of 37, she returned to have the frozen eggs thawed and fertilized and have the embryos transferred to her sister who had a previous successful delivery. Her clinical oncologist was opposed to having this transfer to a gestational carrier because he told this patient that she would be dead before her child was old enough to remember her name! Nevertheless, for whatever time she had left, she wanted to enjoy a child with her husband, and her husband was 100% in favor of having a child.

During the earlier time, when we cryopreserved her eggs we discussed with her, her mother, and sister (both nurses) about the possible use of mifepristone. They discussed this option with her oncologist who was not in favor of using mifepristone. As this point her tumor was only 40% positive for the ER and was negative for the PR.

The oncologist instead chose to treat her with alpelisib. Alpelisib did not seem to halt disease progression, and she suffered from bowel obstructions which was only temporarily relieved by surgery. The oncologist told her it was time to stop anti-cancer and enter a hospice program. Wanting to spend more time with her husband, child, sisters and brothers, and parents, in lieu of hospice, she now wanted to try single agent mifepristone. Her oncologist, who stopped the alpelsib because it was not only failing to halt disease progression, but was causing a bothersome rash, decided he would not "allow" her to take the mifepristone by itself but placed her back on alpelisib. She became markedly hypokalemic on this drug combination, and it became clear that alpelisib interfered with the metabolism of mifepristone so that it now blocked the glucocoidicoid receptor and caused high serum cortisol levels and hypokalemia.

Alpelisib was stopped and she stayed on mifepristone and her potassium returned to normal. After one month on single agent mifepristone, she stated that this was the best quality of life she has had in several years. Despite having a decent quality of life, her oncologist finally convinced her to stop the mifepristone and enter hospice because her tumor markers were increasing despite the treatment with mifepristone. She finally gave in, entered hospice, and died three weeks later at age 39 [17].

This case supports the contention, and frustration, that for whatever reason, clinical oncologists are reluctant to use mifepristone. Thus, they tend to make poor decisions that do not appear to be in the best interest of the patient, at least when the cancer has become very advanced. The oncologist thought she developed either a pituitary adenoma or adrenal adenoma causing her to have Cushing's syndrome. Medical endocrinologists, familiar with the use of higher dosages of mifepristone used to treat Cushing's syndrome would have realized, as we did, that probably the alpelisib was interfering with the metabolic clearance of mifepristone causing a blocking effect on the glucocorticoid receptor and thus recommend to stop the interfering drug which was not needed in the first place. The oncologist was not going to pursue the hypokalemia further hoping it would hasten her death. An endocrinologist who is prescribing mifepristone would not have stopped the drug while she was feeling so much better, gaining more quality time with her friends and family just because her tumor markers were increasing!

Metastatic Fibroblastic Osteosarcoma [29]

A 46-year-old man was diagnosed with a 6 cm fibroblastic osteosarcoma of his right tibia. Following surgery, he was given a chemotherapy cocktail of doxorubicin, cisplatin, and high-dosage methotrexate for nine months. He suffered from many side effects during treatment. Despite this therapy, the tumor recurred in the same area as where previously resected, and now two metastatic lung lesions were found.

He had a second resection of the tibial lesion and was given iodamide and etoposide for nine months alternating with high dosage methotrexate. The chemotherapy was stopped because it did not halt growth of the metastatic lung lesions, and new right tibial tumors were found. Furthermore, Foundation I testing suggested that he may respond to targeted therapy with regorafenib. Nevertheless, CT scans eight months later after regorafenib showed continued disease progression. He now had four lower left lung lesions and the right upper lung lesion increased in size. He also was found to have a metastatic lesion to the ischiorectal fossa, one in the right lower leg, and a large 5 cm lesion in the right pelvic fossa.

Though regorafenib was better tolerated than previous chemotherapies, he was suffering from significant neuropathy pain in his hands and feet as a side effect, plus somnolence. His oncologist suggested he stay on this therapy because there were no more treatment options, and perhaps the regorafenib reduced the rate of the spread.

The patient decided to be treated instead with oral mifepristone. The oncologist insisted that if he was to try mifepristone, he must stay on the regorafenib. Radiologic evaluation for five months on combined therapy for the first time found no disease progression. The patient, against his oncologist's advice, stopped the regorafenib and the neuropathic pain disappeared three weeks later.

The patient was feeling much better on single agent mifepristone and was able to partake in the activities that he enjoyed most national and international travel He did decide to have a radical resection of the mass in the ischiorectal fossa, his right pelvic lesions, and his right leg osteosarcoma.

His good quality of life persisted for four more years. However, there was now evidence of recurrence in the tibia. His medical oncologist advised him of a new drug for osteosarcoma, and suggested he try the new medication. He also advised him to stop the mifepristone because one cannot be sure of drug interactions. Furthermore, this way they could evaluate the efficacy of the new drug. He was advised that if it was not working, the drug would be stopped, and mifepristone resumed.

His wife had remembered our conversation stating that once one stops the mifepristone the cancer will rapidly spread. She begged her husband not to stop the mifepristone. Nevertheless, he decided to give the new drug a try. The cancer spread rapidly, and he died three weeks later.

Obviously, this case further supports the contention that endocrinologists, not oncologists, are best suited to administer mifepristone. This case emphasizes the fact that there seems to be a certain bond and trust that occurs between patient and oncologist, that even when the patient sees marked benefit from the mifepristone treatment , and admonishment about the risks of stopping mifepristone once started, and with a strong reminder from his own wife who is a nurse not to stop the drug; the patient adhered to "his oncologists advice." What is even more worrisome was that the wife told me that she mentioned to the oncologist that rapid spread could occur from stopping the drug, but he did not pay attention to what she was saying nor call us to get our opinion.

Though up to this point, I have described some near-death patients who had a dramatic improvement with mifepristone, who not only had palliative benefits, but longevity, case reports only sug-

gest that a given treatment can work, but perhaps only in a minority of cases. However, in our experience most end stage patients with cancer showed palliative benefits with extension of life. The man with the fibroblastic osteosarcoma was someone who was stage IV with no other treatment options, but who was not extremely close to death. This shows that mifepristone should be considered not necessarily as the last treatment option, but when there are no longer any good alternative treatment options. Patients may turn to endocrinologists before continuing therapy with their clinical oncologist when word spreads through social media that there is another treatment option that seems to work in a large variety of cancers, and that allows you to be treated strictly as an outpatient. Even further testing of disease progression may not be needed. This would provide immense cost reduction for healthcare. Widespread use by endocrinologists may help to influence the manufacturer to reduce the cost of the tablets because the patient will have to take it daily, not just once as for an abortion, for hopefully many years. Since re-purposing a drug is far less expensive than getting a brand-new drug to market since the bulk of the expense to get a new drug to market is establishing safety, the manufacturer of mifepristone or generic companies could try to set FDA approval for cancer use [29]. Daily use of an even higher dosage of mifepristone (>300mg/day) did gain FDA approval for the treatment of Cushing's syndrome, but this dosage is cost prohibitive ($500 per pill off-label).

For a short time, the FDA eased up in granting compassionate use IND approval for this drug. However, with the resumed controversy about mifepristone and pregnancy termination, it has been harder (and almost impossible) to get a compassionate use IND for the drug. COVID made availability of the drug easier for patients allowing mail order for pregnancy termination. Though mail order has been rescinded, mifepristone can now be prescribed by a treating physician for off-label use, but the pharmaceutical company can only send it to the treating physician. Thus, the physician must purchase the drug which costs about $42 per pill, and then the patient can purchase the drug from the doctor. It is my belief that if there becomes widespread use of mifepristone, the endocrinology community could negotiate a considerable reduction in medication charges related to a much larger use of this drug. Some states are now allowing the drug to be purchased at local pharmacies, but they are only providing the kit containing misoprostol which, of course, is not needed.

Non-small Cell Lung Cancer (NSCLC) [30-33]

Recounting these interesting cases of various types of advanced cancers that had very good palliative benefits from single agent mifepristone establishes the fact that PR antagonists/modulators can be a very effective treatment for advanced cancer. However, with individual cases one does not know as to whether this response was found in a very small minority of cancer or the majority. In this perspective the author is attempting to present the cases of practically everyone that we have ever treated with the drug, mifepristone. One woman who was not mentioned had advanced breast cancer whose oncologist kept advising her not to take the drug. When she was extremely moribund, he finally agreed to it. However, it was too late. She took one pill and died the next day. Another patient with NSCLC cancer taking fentanyl was told that he should change the opiate because mifepristone may potentate the effect of fentanyl leading to overdose or even death. He did not heed our suggestion and took mifepristone and fentanyl together and became very somnolent. He elected not to continue the mifepristone rather than stop the fentanyl.

Nevertheless, to better convince the medical community to use this drug, demonstration of efficacy in a larger series would certainly be more credible. We applied to the FDA for an investigator-initiated study to evaluate single agent mifepristone (in this case 300 mg per day because we convinced Concept Inc to provide the drug gratis for advanced NSCLC). The 300 mg dosage is approved for Cushing's syndrome in the United States, but not for abortion. Thus, it did not require a compassionate use IND from the FDA, but it is cost prohibitive.

The FDA approved a 40-patient study. They approved two principal investigators (PIs). What happened next solidifies the position that oncologists are not interested in an anti-cancer drug unless there is some financial reward for the oncology group rendering treatment. Concept Inc was willing to provide the drug gratis but not to provide any financial support for the PIs, despite multiple phone calls, and emails, we could not find one PI. We even implored the American Cancer Society and The American Society for Cancer Research to provide names of possible PIs. They did supply names, but all refused to be a PI. Even our own medical school and hospital, with a large oncology division, turned down the opportunity to be a PI. Thus, by default, the author became the sole PI.

The clinical trial was published in clinical trials. Gov. Our first enrolled patient in the study was referred by the father of one of our OBGYN residents. This OB-GYN resident was cognizant of our work with mifepristone and advanced cancer because of her interest in becoming a reproductive endocrinologist/infertility specialist. She had taken several electives with our practice.

Thus, the clinical oncologist referred a 68-year-old male with stage IV NSCLC with metastasis to the brain [30]. Despite several chemotherapy regimens, his lung cancer progressed with no other tumor markers present so there were no other treatment options. He also had a history of bladder cancer and chronic obstructive pulmonary disease (COPD) from heavy smoking. His main symptomatology was marked fatigue, dyspnea on exertion, and severe cough.

After one month of mifepristone therapy, he stated that he had marked improvement of his fatigue, dyspnea on exertion, and cough. He stated that he had not felt this good for ten years. He was able to resume his job in a band that required him to stand and do some dancing for several hours at a time. Several of his metastatic lesions remained stable and some regressed. However, his primary lung lesion, which had returned prior to starting mifepristone therapy, continued to grow very slowly.

He still felt great after two and a half years. However, he had a consult with his oncologist, and he was advised that nivolumab had been approved for NSCLC even if the tumor marker called pro-

grammed death-1 (PD-1) or programmed death ligand 1 (PD-L1) was not present. He suggested that since the primary lesion was growing, maybe he should stop the clinical study and get nivolumab a check-point inhibitor. The patient, not the oncologist, asked our opinion. I suggested not to stop the mifepristone, and based on the nature of the study he could not add nivolumab. He could stop the study, add nivolumab, pay out of pocket for 200 mg of mifepristone, but he chose to stay on single agent mifepristone. He died after five and a half years later since starting mifepristone, still feeling good, and having a normal functional life. He eventually died of pneumonia during the early phase of the COVID pandemic [30]. During his treatment, he never developed any recurrence of brain metastatic lesions or any new lung lesions.

The second patient enrolled in the study with Stage IV NSCLC lung cancer that progressed not only with standard chemotherapy, but also with nivolumab, which was given because her cancer was weakly positive for the PD-1 marker. She was 66 years old, and her health was also very compromised by severe COPD.

For twelve months of single agent mifepristone therapy, she had a very good quality of life with full resumption of normal activities. Her quality of life began to slowly deteriorate after twelve months of mifepristone treatment, not related to tumor progression (which showed no progression and some tumor regression) but related to worsening of her COPD. She died one and half years on mifepristone therapy, not from cancer progression, but COPD [31].

Case 1 of NSCLC re-emphasizes our contention that despite observing marked clinical benefit, oncologists are quick to add another drug e.g., nivolumab, even though the data did not show a great response if PD-1 is not present or even with low positivity for the PD-1 marker [32]. The oncologist received all my monthly notes about the patient including reminders that stopping mifepristone therapy may result in very rapid tumor progression. The author has never received another referral from this oncologist.

It should be noted that these two patients in our clinical trial would have never been considered eligible for pharmaceutical company-initiated studies. Pharmaceutical companies want to get their drug approved, so most studies would have rejected case 1 because of his history of bladder cancer is a second primary cancer and severe COPD. The fear from the pharmaceutical industry could be if the drug was helping the lung cancer, but if his bladder cancer progressed, and he died from bladder cancer, that could have an adverse effect on the mortality statistics for their drug and inhibit FDA approval. Similarly, the COPD in case I and 2 would have precluded them from eligibility for some pharmaceutical company-initiated clinical trials.

Enrollment into the study was poor. It was clear we would fall short of any type of large series, nowhere near the 40 approved patients. A 59-year-old woman and 46-year-old woman decided to enroll to treat stage IV NSCLC positive for the EGFR mutation that usually responds so well to the third generation tyrosinekinase inhibitor osimertinib. However, their cancer progressed after about a year of osimertinib treatment to stage IV cancer with multiple brain metastases. We advised them not to enroll in the study, but we would apply for a compassionate use IND and use the 200mg dosage rather than the 300mg dosage that we used for the investigator-initiated study. Though they would have to pay for the mifepristone, they would do all their treatment at home rather than travelling monthly to our office to be evaluated and to be provided with the next month's allotment of pills. Thus, they could be evaluated by telehealth. The cost of travelling for these women who lived 1000-2000 miles from our office would far exceed the cost of the drug ($600 per month with 50% reduction when a compassionate use IND is obtained.) They are both alive and doing well five years on single agent mifepristone [33].

Leiomyosarcoma

Another sarcoma responding well to mifepristone was a metastatic leiomyosarcoma. A 45-year-old woman with widely metastatic leiomyosarcoma was found to have lung metastases two years later. Following right lung tumor resection, letrozole was given because the tumor was ER positive. The letrozole did not halt new lung metastases so she was treated for 5 months with 7 cycles of gemcitabine/docetaxel. Despite this therapy, progression of the lung metastases continued, and tumors were resected in both lungs. The patient then underwent bilateral oophorectomy. The cancer progressed despite treatment. She was then treated with mifepristone. For the first time the lesions decreased in size dramatically and had mostly disappeared. Furthermore, she regained her energy and her breathing improved. After six months some lesions started to reappear. Seeing this, her oncologist concluded the cancer was now refractory to mifepristone and stopped the medication and started her on some other chemotherapy regimen (not known). She died of complications from this new regimen.

Again, the oncologist is unfamiliar with the fact that in contrast to other anti-cancer agents the recurrence of some cancer lesions is still consistent with significant extension of a good quality of life. As seen in other cases the oncologist opted to try another regimen which led to a sudden death rather than a likely continued good life if the oncologist just kept her on the mifepristone.

Small Cell Lung Cancer (SCLC) [34]

A 59-year-old male consulted us because of rapid progression and poor quality of life despite standard chemotherapy and immunotherapy with SCLC. Two months after starting mifepristone, there was evidence of regression of some of the metastatic lesions. However, more importantly, his quality of life returned to normal, which included skiing and scuba diving. His good quality of life continued for one year.

However, at the one-year mark, a CT scan showed slight growth of the right upper lung lesion but without pleural effusion, pleural nodularity or interlobular septal thickening that had been present prior to mifepristone therapy.

Though he had been told that slight growth of primary lesions with mifepristone therapy is common, and prolonged quality of life still usually ensues, he was also reminded of the usual rapid

progression of the cancer if mifepristone therapy is stopped. The author sent the oncologist (to whom he never had any personal contact and who never seemed interested as to why was he doing so well on a PR antagonist despite having a tumor not associated with a nuclear PR) all the notes and records of conversations with this patient.

The oncologist convinced him to stop mifepristone and to be treated with a new experimental drug that targets PD-L1. The cancer rapidly progressed and did not respond to the new drug. He died three months later. He never called to ask to retry the mifepristone. I spoke to a friend of his, who thought he did not think his friend was in a state of proper mentation to consider going back on mifepristone once he started the new drug and the tumor spread so rapidly [34].

This case certainly provides more convincing evidence that biases and potential personal gains preclude most clinical oncologists from making the right decision as to what is best for the patient and not for themselves at least as far as treating patients with end-stage cancer without any other good treatment options. They are not likely to treat with single agent mifepristone even if they are made aware of the considerable benefits, at least in the author's experience which he is sharing. There should be no such conflict for endocrinologists.

Conclusion

The main objective of this commentary/perspective is not only to convince the endocrine community of the efficacy of using mifepristone for advanced cancers, but also to explain why endocrinologists are the hope for propagating the benefit of this very effective, and very well tolerated drug. It would seem that most clinical oncologists want to go for the "cure" of metastatic cancer. However, a "cure" for cancer once it is metastatic does not seem to be likely in the near future. Thus, the aim should be to extend the best quality of life possible and convert cancer to a tolerable, chronic disorder.

Hopefully, if the endocrinologists embrace this treatment concept, and more experience continues to demonstrate marked benefit, as a group they may gain approval of the drug by government agencies for cancer use or convince third party insurance carriers that paying for mifepristone is a lot less expensive than most other anti-cancer therapies. At the worst, there are some patients who can afford $13,000 per year to live longer and have a better quality of life, or even better, if the manufacturer agrees to lower the price, considering daily use for years instead of one single pill needed for pregnancy termination, it will become more affordable.

If indeed the role of the clinical endocrinologists is waning in the medical field because common disorders usually do not require an endocrine consultation and can be handled by physicians in different fields, treating the millions of people with advanced cancer with "immuno-endocrine therapy" may give new life to the field of endocrinology. Furthermore, if higher dosages of mifepristone are found to be more efficacious, the medical endocrinologist is more vested in understanding the consequences of glucocorticoid receptor blockage.

From a research standpoint, researchers in endocrinology can conduct experiments to develop a more pure PR antagonist with little or no antagonism of the glucocorticoid receptor. Lower dosages e.g., 200mg of mifepristone may actually increase the level of another P induced immunosuppressive protein PGRMC-1, whereas higher dosages suppress it. The rise of PGRMC-1 may be responsible for local growth of the primary lesion. Alternatively, endocrinologists may help to develop monoclonal antibodies against PGRMC-1 or for that matter PIBF and then decide whether these therapies are possibly even more efficacious than PR modulators. There is much to learn about crosstalk between PIBF and PGRMC-1 and to learn through which mechanism the presence of the nPR inhibit spread of those cancers that have the nPR present. Research endocrinologists can thus help to develop more efficacious therapies with further study of the role of mPRs in cancer which allows the cancer to spread, and nPRS which inhibits spread, to possibly develop the ideal PR antagonist that will block the mPR while not blocking the nPR if present. The ideal PR antagonist will suppress both PIBF and PGRMC-1 [16,35].

The hope would be that with the demonstration of considerable beneficial effects of mifepristone (or possibly an even more improved PR modulator) that these PR modulators can be evaluated in early disease, especially with their lack of side effects and safety. The FDA gave permission for us to treat a man with multifocal renal cell carcinoma to be treated with mifepristone 200mg/day with a hemi-nephrectomy of his right kidney but sparing of his left kidney despite the presence of 3 malignant lesions rather than subject him to bilateral nephrectomy with subsequent dialysis. He is still alive 24 years later [36].

As a reproductive endocrinologist and medical endocrinologist, the author naturally favors endocrinologists to "carry the torch" for treating advanced cancer with PR modulators. Another logical group of physicians to consider treating advanced cancer with PR modulators would be palliative care specialists who are referred to these cases when there are no more treatment options. In fact, the author was invited to give a talk in London in 2023 at an International Palliative care meeting in the section of palliative oncology. Unfortunately, 4 days before the meeting was to start, it was cancelled since a number of speakers were not able to obtain their visas on time. The actual talk was requested to be published in a nursing journal that covers the meeting. Galley proof for this publication was just recently received [37].

The author was of the mindset that if endocrinologists similar to oncologists do not seem interested in treating patients with cancer with PR modulators or fail to generate referrals from oncologists or other physicians, that perhaps palliative care specialists may be interested. However, the opinion of the author's stepdaughter, who is a board-certified hospice/palliative care physician, is that there are not enough palliative care physicians (only about 350 in the United States) to take on this new area of treatment. Furthermore, by the nature of their practice, they are not set up for office outpatient consultations. There are at least ten times as many endocrinologists. Thus, it is greatly hoped that this perspective will

generate interest in the endocrinology community to become interested in immuno-endocrine therapy for advanced cancer. The term "immuno-endocrine therapy" refers to activating anti-cancer cellular immune mechanisms, which ultimately are responsible for inhibiting cancer progression through endocrinological treatment directed against PRs.

Conflict of Interest

None. Neither the author nor family members or friends own any patents for the use of PR modulators for treating cancer or for that matter any patents whatsoever. The author's only association with Concept INC was that they provided the 300mg tablet of mifepristone for 2 patients in the investigator-initiated FDA approved study for NSCLC. The author has never received any financial remuneration from Concept INC or any other pharmaceutical companies. All costs for presentations and publications and research studies including cancer cell line and adrenal studies were self-pay. The author has never received any financial compensation from pharmaceutical companies. The author and his group had participated in some clinical trials relative to drugs used for controlled ovarian hyperstimulation especially for IVF but never an oncology trial.

A western IRB was obtained for treating patients with advanced cancers with mifepristone. All patients signed permission that their cases could be used for teaching or publications as long as their names were not revealed.

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