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Review

Lung Cancer – Standard Therapy and the Use of a Novel, Highly Effective, Well Tolerated, Treatment With Progesterone Receptor Modulators

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Abstract. *The most recent successful advances in lung cancer therapy have directly and increasingly focused on personalized tumor genetic/epigenetic/immunologic profiling, and the identification and development of novel pharmacologic agents aimed at those mutations [e.g., epidermal growth factor receptor (EGFR), Kristen rat sarcoma viral oncogene homolog (KRAS), anaplastic lymphoma kinase (ALK) and immunotherapy against programmed cell death protein 1 (PD-1) and its ligands] which have extended life and provided palliation for lung cancer-patients positive for these mutations. The objective of this study is to provide a review of the large number of drugs and their efficacy as of 2022, for lung cancer, but also introduce a novel treatment that has the potential, based on one controlled murine lung cancer study and 5 anecdotal human cases, that showed marked palliative and longevity benefits in very advanced lung cancer with no other treatment options, i.e., progesterone receptor (PR) antagonists targeting the immunosuppressive protein, the progesterone induced blocking factor (PIBF). Credibility, however, will only be provided when the efficacy can be demonstrated in a large series of lung cancer cases ideally with certain controls. Thus, the ultimate objective of the review is to interest oncologists with a large population of lung cancer patients to perform a well powered study to corroborate or refute the limited experience to date with PR antagonist therapy.*

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Lung cancer is the second most common form of cancer, and the leading cause of cancer- related death (1-3). Worldwide, the 5-year survival rate for the most common form of lung cancer, *i.e.*, non-small cell lung cancer (NSCLC), representing 85% of all lung cancer cases, is 18.6% for newly diagnosed cases (1, 4). In the United States the 5-year survival for NSCLC is 26.5% and is 21.7% if one includes small cell lung cancer (SCLC) (5, 6).

The 5-year survival depends on the stage of lung cancer. Whereas stage I patients have a 68.4% 5-year survival, the survival rate drops to only 5.8% for stage IV (7, 8). Unfortunately, despite the use of post-operative chemotherapy, 50% of patients with stage IB NSCLC (tumor ≥4 cm) and 75% of stage IIIA will progress to stage IV disease (9). The focus of this manuscript will be on stage IV NSCLC and SCLC. Metastatic lung cancer (stage IV) is presently considered non-curable, and thus the goal of treatment is to improve or maintain quality of life, and to prolong overall survival.

Solid tumors including melanoma, breast, and renal carcinoma can metastasize to the brain, but NSCLC is the most common cancer resulting in brain metastasis (10, 11). An even higher percentage of SCLC metastasize to the brain, but since NCSLC represents the majority of lung cancers (85%), NCSLC accounts for more cases of brain metastases (10, 11). The presence of brain metastases with lung cancer makes an already poor prognosis even more dismal (12).

Non-small cell lung cancer may be divided into three types, with a 40% frequency of adenocarcinoma, 30% with squamous cell carcinoma, and 10% with large cell carcinoma (13). Whereas patients with a history of smoking usually have squamous cell carcinoma, patients with NSCLC without a smoking history are generally found to have adenocarcinoma. Platinum-based chemotherapy is still the standard of care in 2022 with stage IV NSCLC, but unfortunately, the typical median time to progression for patients receiving chemotherapy is approximately 5-6 months with an average survival time of only 10-12 months (14, 15).

Standard State of the Art Treatment for NSCLC

Most recently, especially for NSCLC of the adenocarcinoma type, several oncogenic mutations have been identified that are involved in both NSCLC development and progression. These mutations are known as driver mutations. These include mutations effecting genes encoding for the epidermal growth factor receptor (*EGFR*), Kristen rat sarcoma viral oncogene homolog (*KRAS*), and anaplastic lymphoma kinase (*ALK*) (16).

EGFR mutations are present in approximately 10% of NSCLC cases in North America and Western Europe, and 30-50% of patients with NSCLC in East Asia (17). These mutations have also been linked to particulate matter environmental pollutions/fossil fuel vehicle emissions. *EGFR* mutations, as well as other driver mutations, are more frequent in non- or light smokers, especially with adenocarcinomas, but also with squamous cell NSCLC with a light or no smoking history (18).

The breakthrough development of small molecule EGFR-tyrosine kinase inhibitors (TKIs) has allowed for the first time a treatment for stage IV NSCLC that allows a significant extension of not only overall survival, but also a reasonable improvement in quality of life due to relative low toxicity (19-22). The response to TKIs in eligible patients is so good that this is the one type of NSCLC stage IV where platinum-based chemotherapy is not recommended as first treatment option, but instead, the third generation TKI osimertinib is recommended as the first-line therapy for advanced NSCLC with the common sensitizing *EGFR* mutations in exon 21 L858R and exon 19 deletion, with or without concomitant T790M mutations (18). Even if advanced NSCLC is positive for the programmed cell death protein-1 check-point inhibitor (*PD-1*), or if its ligand (*PD-L1*) is present, osimertinib should still be first line therapy, since immunotherapy with checkpoint inhibitors has very poor response rates for *EGFR* mutated patients (18).

Oral TKIs on the pharmaceutical market that can be used for specific targeted *EGFR* mutations, or other driver mutations, in alphabetical order are: afatinib, alectinib, brigatinib, cabozantinib, capmatinib, ceritinib, crizotinib, dabrafenib, dacomitinib, entrectinib, erlotinib, gefitinib, larotrectinib, lorlatinib, osimertinib, pralsetinib, selpercatinib, tepotinib, and trametinib. A good review of the various targeted mutations that respond to these TKIs, plus other parenteral targeted therapies, is provided by Ettinger *et al*. (23). Osimertinib provides an 80% response rate for NSCLC with *EGFR* exon deletions, EGFR L858R, *ALK* (23). Unfortunately, the vast majority of patients with NSCLC do not have the aforementioned targeted mutations.

Thus, it is clear that for stage IV non-squamous NSCLC that is *EGFR* driver mutation positive, based on the type of mutations, one should treat with a targeted therapy most likely an oral TKI inhibitor. The question arises as to how to treat non-squamous NSCLC that are negative for a driver mutation. Though patients who are positive for *PD-1* or *PD-L1* do not respond well to check-point inhibitors when driver mutations are present, they do respond to check-point inhibitors if they are *negative* for driver mutations. Until recently standard first-line treatment for stage IV NSCLC, whether non-squamous or squamous cell, was combinations of platinum-based chemotherapy. However, the treatment strategy has changed with another breakthrough development, *i.e*. immunotherapy with check-point inhibitors.

Some of the check-point inhibitors presently on the pharmaceutical market include pembrolizumab, nivolumab, and tislelizumab which target *PD-1* (23). Atezolizumab targets *PD-L1*. Cytotoxic T lymphocyte associated protein (*CTLA-4*) is a protein receptor that functions as an immune checkpoint and down-regulates immune response. The *CTLA-4* inhibitor ipilimumab has been recently approved, and has been found, when combined with the *PD-1* inhibitor nivolumab, to provide superior results compared to standard chemotherapy alone in NSCLC (24). However, it was not tested against double platinum-based chemotherapy and pembrolizumab (24, 25). Another *CTLA-4* inhibitor, tremelimumab, plus the *PD-1* inhibitor durvalumab, may possibly extend overall survival (26).

Pembrolizumab monotherapy was found to provide superior results compared to doublet chemotherapy when ≥50% of the NSCLC cells on biopsy were positive for the *PD-L1* marker (27). In contrast, the *PD-1* check-point inhibitors nivolumab and durvalumab failed to show the same beneficial effect as pembrolizumab (26, 28). Thus, pembrolizumab is the *only* approved monotherapy for first line therapy for stage IV squamous cell NSCLC or non-squamous NSCLC negative for driver mutations where the *PD-L1* marker is ≥50%. This provides the highest improvement in overall survival, with less side effects, and thus a better quality of life (28).

In addition, another check-point inhibitor, atezolizumab, was found to increase overall survival better than standard platinum-based therapy when used as monotherapy in patients with high *PD-L1* level ≥50% (29). Drug approval for first line therapy may be granted in the near future.

Thus, to summarize, the thought process used by many oncologists to treat metastatic stage IV lung cancer is that if the patients have a driver mutation, then a specific oral drug,

e.g., the TKI osimertinib, should be given as first line monotherapy. If the cancer is positive for *PD-L1* ≥50%, pembrolizumab should be prescribed as first-line monotherapy. For patients healthy enough to withstand chemotherapy, triplet regimens with platinum doublets and pembrolizumab or atezolizumab may be given even if the *PD-L1* is negative, but check-point inhibitors work better with some degree of the presence of the *PD-L1* marker (27, 30). Some regimens even add bevacizumab to the treatment cocktail, so this would be considered quadruplet therapy (31).

When these newest options fail, most oncologists now refer the patients to palliative care or hospice, or NIH trials database for investigational regimens, often even more toxic and in the earlier stages of drug development (18). However, there are multiple reports of beneficial effects of using progesterone receptor (PR) modulators, even in cancers such as lung cancers devoid of the classical nuclear PR (nPR) with little to no significant side effects. The PR modulator mifepristone, in particular, has been used as monotherapy, and in combination with osimertinib, for stage IV NSCLC with *EGFR* mutations, without any other viable treatment options and will be discussed below.

The main objective of this review is to familiarize present day treatment options for advanced metastatic NSCLC and SCLC and the relative efficacy of these therapies. Thus, the reader will be familiarized with the most common targets for the development of new therapies when present day therapies fail. To provide this update the authors utilized PubMed and Google Scholar to review appropriate studies on lung cancer therapeutics published in the last 10 years. However, a second very important objective is to familiarize physicians with a less commonly known tumor target, known as progesterone induced blocking factor (PIBF), that may allow lung cancer to metastasize. Even more importantly to familiarize the reader with preliminary data, including one controlled murine lung cancer study, and 5 anecdotal human cases that suggest the potential benefit for a novel therapy with PR antagonists even for these lung cancer tumors devoid of the classical nuclear PR. Nevertheless, credibility can only come to fruition if this preliminary high efficacy can be demonstrated in a large study of patients with metastatic lung cancer with no other standard treatment options available, possibly even with controls, if deemed ethical. Thus, the main objective of this review is to hopefully interest an oncology group who treat a large population of patients with lung cancer to determine the true efficacy of PR antagonist therapy for lung cancer.

Standard State of the Art Treatment for Small Cell Lung Cancer in 2022

Small cell lung cancer represents 15% of lung cancers (32). It occurs mostly in smokers (33). The prognosis is extremely poor related to a high proliferation and metastasis rate (32). Generally, treatment with platinum-based drugs, *e.g.*, platinum-etoposide combination, are given initially, and some tumor regression is usually seen. However, shortly after, the cancer spreads rapidly related to acquired resistance (34). Most of the time, when the diagnosis is made, there is already stage IV disease with metastases to brain, bones, liver and lymph nodes (35).

Recently, new drugs have been approved for treatment of SCLC including check-point inhibitors, *e.g.*, nivolumab or pembrolizumab, for second- and third-line treatments (36, 37). Also, lurbinectedin, an alkylating agent, was approved if advancement occurs despite platinum based first line therapy (38).

The search for targeted molecules for SCLC, *e.g.*, as used in NSCLC, continues, and drugs that inhibit mTOR kinase have been investigated, along with metabolic inhibitors, but to date, most clinical trials have shown limited single agent efficacy (39). Recently, the combination of the immune check-point inhibitor camrelizumab, combined with the anti-angiogenic drug anlotinib, showed promise in a recent case treated in China (40).

The Use of Progesterone Receptor Modulators in the Treatment of Advanced Lung Cancer

Treatment with PR modulators anecdotally, *e.g.*, mifepristone, have shown excellent beneficial effects on both extension of quality of life in patients with stage IV NSCLC, and probable SCLC, despite no more standard treatment options available (41-45). The target for mifepristone, a PR antagonist/modulator, is an immunosuppressive protein known as the PIBF used by a variety of different cancer types, and also used by the fetal-maternal unit to escape cellular immunity especially by natural killer (NK) cells through stabilization of perforin granules and granzymes, and also cytotoxic T-cells (46-49).

Two of the 5 cases reported were the first two patients registered for a United States Food and Drug Administration (FDA) that was approved as an investigator-initiated investigative new drug approval (IND) study to treat up to 40 patients with stage IIIB or IV NSCLC that had progressed despite a minimum of two chemotherapy or immunotherapy regimens ("A phase II study of treatment with oral mifepristone as salvage therapy in patients with advanced or metastatic non-small cell lung cancer who have failed two or more chemotherapy regimens", https://clinicaltrials.gov/ct2/show/NCT02642939).

Case 1. A 68-year-old 50-pack/year smoker presented with stage IV NSCLC of the adenocarcinoma type with bilateral lung lesions and brain metastases (41). His first treatment included carboplatin/bevacizumab, docetaxel. Subsequent treatments included pemetrexed, then gemcitabine/carboplatin doublet, and palliative radiation therapy for his brain lesion.

He had no targeted mutations for *EGFR* mutation or *ALK* rearrangement or *PD-L1*. With no other treatment options available, he enrolled for treatment with single agent 300 mg daily mifepristone. Within a short time, he claimed he felt better than he had in the last 10 years. He was able to resume his job in a band where he stood for hours at a time. He still was asymptomatic two and a half years later, except mild dyspnea on exertion, related to his chronic obstructive lung disease (COPD), when his largest lesion, that had remained stable, started to grow. His oncologist suggested now with progression he should consider stopping the mifepristone study and be treated with nivolumab, which was now allowed to be given even if the *PD-L1* marker was absent (41).

We advised him that with our experience with other cancers treated with mifepristone, when a lesion started growing it is not a harbinger of incipient rapid spread, but generally grows slowly, and the patient remains in good health. His chose to stay on the mifepristone. He continued good health working full-time for the next three years without evidence of recurrent brain lesions or new lung metastases or metastasis to liver or bone. He died at age 73 from complications of pneumonia which may have been related to his COPD, though the lung cancer could have contributed to its development also. It should be noted that his pre-existing papillary urothelial carcinoma, that had been resected, never reoccurred (41).

Case 2. The second case of single-agent mifepristone therapy 300 mg/day who also enrolled in the aforementioned FDA investigator-initiated therapy, was a 68-year-old woman with adenocarcinoma of the lung. Her stage IV lung cancer at the time of enrolling in the study was complicated by very advanced chronic obstructive lung disease (42).

Her prior therapy consisted of carboplatin, pemetrexed, bevacizumab combined therapy followed by carboplatin and docetaxel. She then was treated with erlotinib. She was negative for targeted *EGFR* mutation or *ALK* rearrangement. She was not tested for *PD-L1*. With continued progression, she was treated with 11 cycles of nivolumab. She showed some stabilization of the cancer initially, but by 11 cycles the cancer was rapidly progressing again.

She was started on oral 300mg mifepristone daily. There had been no disease progression based on CT scans after 18 months of single agent mifepristone therapy. In fact, some metastatic lesions regressed in size. She had been able to resume physical activity that was not possible for the past two years. However, her COPD progressed to end-stage disease. She died a couple months later, not from her lung cancer, but her COPD (42).

Cases 3 and 4. Two women, one aged 59, and the other 46, with stage IV NSCLC, both positive for *EGFR* mutations, applied to be part of the study. Both of these patients had been treated by single agent third-generation TKI osimertinib which did provide inhibition of tumor growth for about one year. However, when the cancer started to resume growth as evidenced by new lesions and growth of arrested lesions the patients opted to have mifepristone added to their osimertinib therapy. Related to large geographical distances that would be required on a monthly basis and the possibility that there could still be some benefit from continuing the osimertinib, we elected to not treat them with the investigator initiated study but apply for compassionate use 200 mg mifepristone. With combined usage of osimertinib and mifepristone, both are still alive and doing well after four years of treatment. It should be noted that both had multiple brain metastases and bone metastases. There has been no progression of their cancer in four years, and no progression of brain metastases, no new ones, and no neurological symptoms (43).

Case 5. Another case of lung cancer, who responded extremely well to 200 mg/daily oral mifepristone, was a 78-year-old woman with chronic lymphocytic leukemia who developed sudden severe dyspnea on exertion and marked fatigue (44). On admission to the hospital, her PO_2 was 72 mmHg, and her serum sodium was 118 mmol/l (45). A chest x-ray revealed extensive pulmonary nodules with a diagnosis of metastatic lung cancer. Though she refused a lung biopsy, because she realized she was terminal, and no standard therapy was likely to extend her life, the presumptive diagnosis, based on the rapidity of symptoms (there was no evidence of lung cancer in a chest x-ray performed 3 months before) coupled with the severe hyponatremia (probably related to the syndrome of inappropriate anti-diuretic hormone) was SCLC, though NSCLC was still a possibility (45).

Because of lack of significant side-effects of mifepristone, she agreed to be treated with 200 mg oral mifepristone daily. She was much improved after two weeks of single agent mifepristone therapy. After one month on treatment her PO_2 without any oxygen supplementation was 99-100 mmHG and her serum sodium returned to normal at 145 mmol/l (45).

After two months of treatment her axial CT showed mostly complete resolutions of all of her lung nodules. The few remaining nodules were much smaller. Subsequent chest x-rays over the next five years demonstrated no pulmonary nodules, just a ground glass appearance to the lungs. Her PO_2 and serum sodium continued to be normal. She died of a myocardial infarction at age 83 (44, 45).

Case 6. There is a case at present of a 68-year-old man who has surgically demonstrated SCLC, who was treated with mifepristone. Initially, he had been diagnosed with NSCLC with *EGFR* mutation deletion 19 and did well for one year with treatment with 80 mg osimertinib. However, cancer recurrence occurred. Repeat biopsy now showed that the resistance to osimertinib was related to conversion to SCLC. He has been treated for over one year with oral mifepristone,

and despite slow progression, he still feels quite well and is able to enjoy activities, *e.g.*, scuba diving and skiing.

With the terrible prognosis with present day anticancer treatment for SCLC, and the very good response in one patient with probable SCLC and severe hyponatremia, and this 68-year-old man whose NSCLC converted to SCLC doing very well, following single agent mifepristone, it is our opinion that this PR antagonist should be first line treatment for SCLC, especially because it is also well tolerated. Hopefully, this publication will generate interest in an oncology group to conduct a larger study on patients with SCLC.

It is clear by the above small case series that mifepristone can be effective in some cases of advanced lung cancer. However, other physicians reading these case reports are without knowledge as to whether these cases are the exception rather than the rule, as they were not part of any large randomized double-blind placebo-controlled trial. Assuming that the hypothesis is correct, that mifepristone's main oncologic benefit is *via* suppressing PIBF, what if only a small percentage of lung cancers use PIBF to proliferate and avoid immune surveillance (46-50)? Notably, the cases mentioned here are the majority of cases we have treated.

Unfortunately, despite free medication, we were not able to recruit anywhere near the 40 patients allowed for our NIH approved salvage study on patients with advanced NSCLC, we believe due greatly to protocol requirements, and financial issues. This study required a one-month delay in treating with mifepristone from stoppage of previous therapy, to be clear that if a benefit was found, it was from the mifepristone therapy. One woman who was approved was so advanced that she died one day after taking her first mifepristone pill. She was the third patient in the study. The study was terminated when the 68-year-old male died five years later from pneumonia. Since that time, we have instead been using mifepristone off-label with compassionate use from the United States Food and Drug Administration (FDA).

One male receiving palliative care, with very advanced lung cancer, who obtained the 200 mg dosage through a compassionate use IND, stopped the drug because the combination of mifepristone and fentanyl made him lethargic (mifepristone will interfere with the metabolism of fentanyl, and the combination should be avoided when possible). He decided, rather than the option presented to him of switching to another analgesic, or decreasing the dosage of fentanyl, he elected to discontinue the mifepristone (which he only took for two days) and stay on the fentanyl. He died within that month. These 3 patients are the only cases of lung cancer we have treated with 300 mg oral mifepristone daily through the investigator-initiated study which was approved by the FDA for 40 patients.

Unfortunately, for the investigator-initiated study approved by the FDA for 40 patients, it approved only two principal investigators. Furthermore, with no funding available to compensate principal investigators, we were not able to recruit even one oncologist with a large lung cancer patient population, possibly because of competition for patients from multiple well-funded studies for a variety of trials with new anti-cancer agents from pharmaceutical companies for lung cancer. It is our hope that these anecdotal case reports detailed above will generate intertest by the public and by oncologists with a large lung cancer patient population to objectively evaluate mifepristone, or some other PR antagonist, in a larger controlled series.

Our first case report of marked extension of a high-quality life following single-agent treatment with mifepristone despite what appeared to be terminal advanced cancer was first published over a decade earlier in 2009 in a case of colon cancer (51). We have published many other similar anecdotal case reports for a variety of cancers including, but not limited to, thymic epithelial cell, multi-focal renal cell, transitional cell of the renal pelvis, glioblastoma multi-forme, pancreatic carcinoma and fibroblastic osteosarcoma, besides the aforementioned cases of lung cancer. These cases have been previously published (52-56). It should be noted that we purposely chose cancers that were devoid of the classical nPR, since there had been previous studies suggesting that the nPR may help to thwart cancer progression, so that a PR that antagonizes the nPR that slows cancer progression, may in theory, limit the success of suppressing membrane PRs responsible for the production of PIBF (47-51, 57).

A search of the literature failed to find case reports or series either corroborating or refuting these claims of efficacy of mifepristone from other centers for cancers devoid of the classical nuclear PR. Probably related to sensitivity of pro-life groups about approving the first PR antagonist on the market, mifepristone, whose sole approved use was as an abortifacient, the United States FDA limited prescribing rights to only licensed abortionists, and precluded off-label use without obtaining a compassionate use IND. Initially, the INDs were cumbersome and time consuming, but then for a period of time the obtaining of a compassionate use IND became more streamlined. However, in the last year or two, obtaining a compassionate use IND has become more difficult again. At first, we thought this was related to the COVID pandemic, and the lack of personnel in the FDA, but this may also have been related to anticipation of the Supreme Court's decision on Roe *vs*. Wade. With the recent Supreme Court's decision in Dobbs to overturn Roe *vs*. Wade, we believe it will prove even more difficult to obtain FDA permission for compassionate use of mifepristone, and certainly our hopes that the FDA would observe such beneficial effects of mifepristone for advanced cancers that they would lift the ban on off-label use, at least to board certified oncologists, no longer seems realistic. This may apply to larger controlled or observational studies also of mifepristone as potential "anticancer immune therapy" for multiple genetically, pathologically, and immunologically diverse but deadly tumors.

When other PR antagonists became approved for other uses than therapeutic abortion, *e.g.*, telapristone in Europe and ulipristal in the United States, we considered trying ulipristal for advanced cancers which would have the advantage of lack of side effects from adrenal insufficiency because, in contrast to mifepristone, these PR antagonists have little antagonistic effects on the glucocorticoid receptor. Nevertheless, we did not try ulipristal because of how well the patients were responding to mifepristone, and without knowledge of what dosage of ulipristal to use in cancer. Also, we were not sure that there could possibly be some beneficial effect in having mild suppression of the glucocorticoid receptor by mifepristone.

Thus, we planned to test other PR modulators, *e.g.*, ulipristal and onapristone in vitro to see if they can suppress PIBF similar to our studies over the last 30+ years of mifepristone suppressing PIBF in leukemia cell lines, and its broader effects on the immune system, including cytokine expression and NFKB signaling (58). These studies would also eventually determine the relative efficacy of mifepristone vs. ulipristal vs. onapristone in suppressing another progesterone induced immunosuppressive proteins, also used by malignant tumors to escape immune surveillance *e.g.*, the progesterone receptor membrane component protein (*PGRMC*) (1 and 2) (59). There is some evidence that in the dosages used, mifepristone may actually stimulate, rather than inhibit *PGRMC-1*, which may decrease some of the efficacy of suppressing PIBF (57). The ideal PR modulator would be one that suppresses both PIBF and *PGRMC-1*, and possibly *PGRMC-2* (which seems to be utilized less than *PGRMC-1* in various tumors (57).

The 300 mg dosage of mifepristone is not approved for therapeutic abortion, but for the hyperglycemia of Cushing's syndrome. One can obtain the 300 mg dosage without FDA approval. However, the cost is prohibitive (once daily 200 mg mifepristone costs about $500 per month in the United States, and even as low as $30 a month in some countries, whereas the 300 mg dosage will cost approximately $15,000 per month). For some reason Corcept, Inc. did not seem interested in trying to repurpose 300 mg mifepristone to treat cancer as evidenced by their failure to provide any additional funding to attract one or two principal investigators. The most expensive part of getting a drug to market are the phase I and II trials and the part that contributes the most time to reach the market (generally 7-10 years). Starting with phase III the cost would be only a tenth of the cost of starting with safety trials and would take only 2-3 years to reach the market. The 300 mg dosage of mifepristone on a daily basis has proved safe and has already passed phase I and II drug trials, and thus repurposing could start with phase III. We do not believe that the 300 mg dosage mifepristone was approved in Europe for treating Cushing's syndrome. Perhaps demonstration of positive benefit of ulipristal in anecdotal cases for advanced lung cancer (or other cancers) could convince the pharmaceutical company producing ulipristal to consider repurposing the drug.

After conducting the leukemia cell line studies on efficacy of various PR modulators on PIBF and *PGRMC-1* secretion, our group was planning to once again try to get FDA permission to treat stage IV lung cancer with either the 200 mg dosage mifepristone, or ulipristal, or onapristone in a larger series depending on their respective abilities to down regulate PIBF (or *PGRMC-1*). Ulipristal is approved as "the morning after pill", but interestingly, it has no FDA restrictions for off-label use because it was not approved for therapeutic abortion. We presently have one woman with stage IV treatment resistant NSCLC, who was considered close to death, that is doing well after three months of treatment with 15 mg daily oral ulipristal. We were forced to try 15 mg per day ulipristal ahead of the aforementioned cell line studies because of the increased difficulty in obtaining mifepristone. Off-label use of ulipristal does not require FDA permission to use it. We chose 15 mg over 30 mg to save the patient money (approximately $650 per month for 15 mg daily).

The PR modulator onapristone is presently not available for clinical use on the pharmaceutical market. However, renewed interest in onapristone has resurfaced with the rights to research the drug bought by another pharmaceutical company. There are multiple clinical trials ongoing evaluating the efficacy in cancer that have positive nPRs, *e.g.*, breast, ovarian, endometrium and prostate. The pharmaceutical company is trying to create a new form of onapristone with greater purity, especially an extended release form, that will reduce liver toxicity, which is why the continued studies to gain approval for this drug were stopped, *i.e.*, a rise in liver enzymes (60). Demonstration that onapristone can suppress PIBF using leukemia cell lines might encourage the pharmaceutical company sponsoring the trials with cancer that have positive nPRs (which according to our concept is least likely to be effective) and sponsor a trial with onapristone for lung cancer, either advanced or earlier (57).

As mentioned, one advantage of ulipristal, or onapristone, over mifepristone is that they have little or no suppression of the glucocorticoid receptor. Thus, they are not likely to cause symptoms of adrenal insufficiency or hypokalemia when used in larger dosages. Certain drugs may interfere with the metabolism of mifepristone, leading to higher concentration of the drug, and thus adrenal insufficiency and hypokalemia. Thus, if certain anticancer drugs are to be considered in combination with a PR antagonist, ulipristal or onapristone are less likely to cause such significant adverse events (61). For lung cancer however, mifepristone has been used without consequence in patients taking osimertinib and platinum-based chemotherapy (43).

Another way to compare relative efficacy of these three PR modulators in thwarting cancer would be to go back to animal studies. A controlled study using A/J mice bred to have a high

frequency of lung cancer were treated with the weight equivalent of 200 mg/day of mifepristone for human treatment, given by gavaging the animals *vs*. controls using the olive oil medium (62). The data showed that 67.4% of the mice treated with mifepristone survived one year *vs*. 27% of the controls ($p<0.05$, chi-square). Even more impressive, 66.7% of mifepristone-treated mice had no "sick days" (body conditioning scores <4%) *vs*. none of the controls, consistent with the human experience) (62). Mice with spontaneous lung cancer could be divided into those receiving mifepristone, ulipristal, onapristone, and olive oil control to compare relative efficacy of drugs to help decide which one to choose for human treatment.

Thus far, the PR modulator mifepristone has demonstrated efficacy in SCLC and NSCLC without any known driver mutations, and with two different types of *EGFR* mutations. Related to relatively low amount of side effects to osimertinib, or other third generation *TKI* inhibitors, it would make sense to start patients with the *EGFR* driver mutations on third or fourth generation *TKIs*. The question arises, based on these two cases doing very well with mifepristone therapy when osimertinib was beginning to fail, and the fact that the two drugs did not seem to have any negative interactions, should one start both drugs at the same time (43)?

So far, we have not treated a case of NSCLC with *ALK* rearrangements (which accounts for 2-5% of all NSCLC) (63). Similar to *EGFR* driver mutations, *ALK* rearrangements respond well to *ALK TKIs*, *e.g*., alectinib, brigatinib or lorlatinib. These drugs should be considered as first line therapy (64). Non-small cell lung cancer with *ALK* rearrangements have a high percentage of brain metastases already present so one should use *ALK TKIs* as above that cross the blood brain barrier, and thus are superior to earlier *TKIs*, *e.g*., crizotinib (64-68). Similar to *TKIs* for *EGFR* mutations, these second and third generation *ALK TKIs* should be started regardless of the *PD-L1* studies because there is a poor response rate to check-point inhibitor in this population. Thus, it seems reasonable to consider mifepristone or other PR modulators, if progression occurs despite these new *ALK TKIs*, *e.g*., third generation lorlatinib, or if side effects preclude continued use of the *TKIs*. It should be recalled that mifepristone was very effective in preventing recurrence of brain metastases in the three patients with NSCLC and was effective in glioblastoma multi-forme stage IV (41, 43, 54).

For advanced NSCLC in patients without insurance coverage in the United States, or who are not healthy enough to tolerate chemotherapy, we would suggest starting the PR antagonist as first line therapy. This would be made possible if the governmental agencies dropped the unfortunate, ban on off-label use of the much less expensive 200 mg dosage of mifepristone. If not, for about $650 per month, oral ulipristal 15 mg tablets can be tried especially if future studies continue to demonstrate as much or even more efficacy than mifepristone.

In certain large Asian countries mifepristone is much less expensive, and they do not have any restrictions in using the drug for oncologic use. However, we are not aware of any ongoing studies in Asia using the drug. In Europe, there were no restrictions for using drugs off-label, but mifepristone, because it is an abortifacient, has restrictions imposed by many European countries, similar to the United States. Since the Dobbs decision, there has been increased interest in overseas direct mail order of mifepristone for self-managed abortion at low/no cost from countries without such legal limitations. Whether this would be one avenue for American patients facing fatal cancers who wish to try mifepristone is not impossible. Yet, we would argue that the drug should be treated as a promising advancement in cancer therapeutics deserving an objective and decisive study/studies to evaluate it on its safety and efficacy in oncology, separate from pregnancy and abortions politics.

As of 2022, most oncologists would agree that for patients with NSCLC with >50% of the cancer cells positive for *PD-L1* (referred to as *PD-L1-high*) that not only is single agent treatment with the check-point inhibitor pembrolizumab, atelozolizumab, and cemiplimab-rwlc approved by the FDA for first line treatment for NSCLC, rather than platinum-doublet chemotherapy, but the studies comparing the two have found significant improvement with overall survival (OS) with single agent check-point inhibitors (69). In the keynote-024 study, pembrolizumab was given at 200 mg I.V. once every three weeks until 24 months, unless there had been unacceptable toxicity, or disease progression (69). Atelolizumab was given at 1,200 mg *I.V.* every three weeks, unless the patient had unacceptable toxicity or disease progression (69). Cemiplimab-rwc 350 mg was given I.V. every three weeks until 108 weeks unless unacceptable toxicity, or disease progression occurred (69).

Previous studies with pembrolizumab showed a median OS of 30.0 months but the OS for the keynote-024 study was not recorded as yet. For atezolizumab the OS was 20.2 months *vs*. 13.1 for platinum-based chemotherapy, and for cemiplimab the OS was 22.1 months *vs*. 14.3 for platinum-based chemotherapy (69).

It should be noted, however, that though so far only 5 patients who have taken the mifepristone for at least 18 months, the median OS cannot be recorded because 2 of the 5 patients are still alive (and doing well), but if they suddenly died in the near future the OS would be 48 months, and that is despite the fact that the mifepristone was not started nearly as early in the cancer state as they would have been started if they were part of the three FDA approved studies mentioned above. In fact, they were not started until there was significant progression with platinum-based chemotherapy, check-point inhibitors, or third generation *TKI* inhibitors.

Thus, despite the small number of cases, started to date, with PR antagonist/modulators for lung cancer, even though

we do not have a documented case of a patient with *PD-L1 high* NSCLC, it would seem reasonable to evaluate the efficacy of check-point inhibitors alone *vs*. check-point inhibitor plus PR antagonist/modulator from the start vs. check-point inhibitors initially with PR antagonist added at the start of cancer progression *vs*. check-point inhibitor initially, switching to mifepristone, or other PR antagonist, once there is evidence of disease progression.

The same type of study could be considered for NSCLC with the *PD-L1* marker present in <50% of the cells, where first-line therapy would be platinum-based chemotherapy followed by check-point inhibitors. The one patient who did fail after progressing with the check-point inhibitor nivolumab, did not have the tumor tested for the *PD-L* marker (42). Thus, we are still searching for cases with the presence of NSCLC with the presence of the *PD-L1* marker, who has progressed despite treatment of the cancer with a checkpoint inhibitor, to see the efficacy of mifepristone, or another PR antagonist in that circumstance.

Since two patients with extensive brain metastases and stage IV NSCLC positive for the *EGFR* mutation who progressed despite osimertinib, are alive and well four years after mifepristone therapy, it would seem reasonable to conduct similar studies, as suggested for NSCLC positive for *PD-L1*, to evaluate different adding times for PR antagonists to osimertinib therapy or other third or fourth generation *TKIs* in NSCLC with *EGFR* mutations.

As mentioned, to date we have not had any experience with patients with *ALK* fusion-positive lung cancers. We look forward to eventually treat with mifepristone, or another PR antagonist/modulator, patients who have progressed with NSCLC despite treatment with the second generation *TKI* inhibitor ceritinib, which is one of the drugs of choice as first line therapy for this type of cancer with brain metastases (70). As pointed out by Chow *et al*., "patients with active brain metastases (untreated) are often ineligible for, or underrepresented, in clinical trials of systemic therapies" (70). Perhaps this was related to the fact that the first generation *TKI* for *ALK* positive NSCLC, crizotinib, had shown only moderate intracranial activity and poor blood brain barrier penetration (71).

About 24-30% of patients with *ALK* NSCLC present with brain metastases at the time of initial diagnosis (72, 73). The prognosis remains poor for patients with all types of NSCLC when there are brain metastases (73, 74). For a drug company to gain approval for an anticancer drug, they need to demonstrate significant positive effects on clinical benefit. Thus, to gain drug approval, pharmaceutical companies may try to enroll patients with a somewhat better prognosis (75). Indeed, certinib did show antitumor activity in patients with *ALK*+ NSCLC with active brain metastases and/or leptomeningeal disease in the ASCEND-7 study (70). As stated by Murciano-Goroff "the trial was unique in that the ASCEND-7 trial only treated patients with central nervous system metastasis. The inclusion of patients with symptomatic brain metastases and leptomeningeal disease was particularly laudable, recognizing that most clinical trials exclude these populations" (76).

It should be recalled that drugs directed against *PD-L1* and *PD-1* do not fare well in *EGFR* or *ALK* positive NSCLC. In view of mifepristone significantly providing a high-quality life in the two aforementioned patients with *EGFR* mutation positive NSCLC, with extensive brain metastases, it would seem reasonable to consider mifepristone for *ALK* positive NSCLC with brain metastases that have progressed despite treatment with ceritinib or other *ALK* inhibitors, *e.g*., alectinib, brigatinib, lorlatinib, or crizotinib, even though, to date, mifepristone has not been tried in patients with NSCLC with *ALK* rearrangements.

Other Mutations in NSCLC and Targeted Therapies for These Mutations

ROS1 rearrangements. *ROS1* rearrangements are present in 1-2% of patients with NSCLC (72). *ROS1* is a receptor tyrosine kinase of the insulin receptor family (77). Patients with NSCLC respond to treatment with crizotinib which is a *ROS1/MET* inhibitor. Certain clinical trials show that treatment with crizotinib may provide a mean duration of response of 25 months (78). One can extend life even further when crizotinib is losing efficacy by treating with lorlatinib (79). Another drug that could also be used to extend life with this *ROS1* rearrangement is entrectinib (80).

Kristen Rat Sarcoma Viral Oncogene Homolog (KRAS)

KRAS is the most common driver mutation in lung cancer and mutations in codin 12 (*KRAS G12C*) mutations representing about 50% of all *KRAS* mutations (81). As previously mentioned, driver mutations, *e.g*., *EGFR* mutations and *ALK* rearrangements are common in non-smokers whereas *KRAS* mutations seems more common in smokers (81).

Initially, there was pessimism about funding a drug to target this *KRAS* mutation in metastatic NSCLC. However, there has been some optimism about sotorasib which specifically and irreversibly inhibits *KRAS G12C* by locking it in an inactive GDP-bound stage (82). Sotorasib has been used to treat patients with *KRAS* mutations with metastatic non-squamous NSCLC that has progressed despite platinum-based chemotherapy (carboplatin/pemetrexed or paclitaxel) with or without immunotherapy. A phase II study found a median overall survival of 12.5 months with a response rate of 37% and grade 3 adverse events in 20% (83).

MET ex 14 Skipping Mutation

Oncogenic driver genomic alterations in *MET* include *MET ex 14* skipping mutations, *MET* gene copy number (*GCN*) gain or amplification, and *MET* protein overexpression (84). *MET ex 14* skipping mutations occur in 3-4% of patients with NSCLC adenocarcinoma and 1-2% of other types of NSCLC (85). First line therapy with the oral capmatinib TKI that selectively inhibits *MET ex 14* skipping mutations found an overall response rate of 68%, with a median progressive free interval of 9.13 months in one study and only 5.42 months in a subsequent study (86). Grade 3 to 4 adverse events occurred in 75% of patients (86). It seems to be effective even with brain metastasis (86).

Tepotinib is an oral TKI that selectively also inhibits *MET ex 14* skipping mutations, but also high-level *MET* amplification (87). The response rate was 46%, progressive free survival was 8.5 months and grade 3 or higher adverse events in 28% when treating *MET ex 14* skipping mutations. Preliminary data for *MET* high amplification showed a 42% response rate. Capmatinib and crizotinib have also shown some beneficial effects in treating high level *MET* amplification (86, 88). The median overall survival in patients with NSCLC (mostly adenocarcinoma) was 11.4 months (88).

RET Rearrangements

RET is a tyrosine kinase receptor that influences cancer cell proliferation and also differentiation. Rearrangements may occur in NSCLC between the *RET* gene and other domains especially kinesin family 5B (*KIF5B*) and coiled-coil domain containing-6 (*CCDC6*), which lead to overexpression of the *RET* protein (89, 90). *RET* rearrangements are most common in patients with NSCLC adenocarcinomas but only represent about 1-2% of all patients with NSCLC (91).

Though cabozantinib has been used as first-line therapy for *RET* rearrangements, success rate with less toxicity has been found with treatment with the oral TKI pralsetinib (92). First-line therapy showed a 70% overall response rate. It was much better tolerated than cabozantinib. Another oral TKI selpercatinib showed an 85% overall response rate when used as a first-line therapy (23).

BRAF Mutations

V-RAF murine sarcoma viral oncogene homolog B (*BRAF*) is a serine/threonine kinase that is part of the AMP/ERK signaling pathway. The *BRAF V600E* mutation occurs in 1-2% of patients with lung adenocarcinoma (23). There are other *BRAF* mutations other than *V600E* but *V600E* is the only point mutation that has a targeted drug therapy (23). It is most frequently found in smokers.

Dabrafinib inhibits *BRAF* harboring *P.V600E* mutations (93). Another drug trametinib inhibits *MEK ½* which is downstream of *BRAF* signaling (86). The combination of these two drugs provided an overall response rate of 64% and median, a progression-free survival of 10.9 months and a median overall survival of 17.3 months and a 22% 5-year survival (93, 94).

Table I lists the various anticancer drugs available for treating NSCLC and SCLC and the various molecules that they target.

2022 Update Biomarker Testing and Subsequent Targeted Therapies by the National Comprehensive Cancer Network (NCCN)

NCCN in their 2022 Version 1 recommends that for NSCLC to perform molecular testing that identifies all of the established actionable driver mutations, *e.g.*, *ALK, BRAF, EGFR, KRAS, P.G12E, MET ex 14 skipping, NTR k1/2/3, RET, ROS1 high-level MET amplifications* and *ERBR2* (HER2) mutations using either a single assay or a combination of a limited number of assays (23).

The NCCN NSCLC Panel recommends upfront testing for *PD-L1*, which is an immune biomarker before first-line therapy in patients with metastatic NSCLC to determine if the patient would likely respond to check-point inhibitors. Actionable driver mutations, *e.g.*, *EGRF* and *ALK* rearrangements, are much more common in patients with metastatic non-squamous NSCLC and NSCLC not otherwise specified (NOS) (23). Nevertheless, some less common actionable driver mutations may be found in some NSCLC of the squamous cell type and thus molecular testing could still be considered.

So far, the only patients with driver mutations that have been treated with a PR antagonist, *e.g.*, mifepristone, have been patients with NSCLC with the *EGFR* mutation (3 patients). One patient who is still feeling great after four and a half years after mifepristone treatment (which was not started until progression on osimertinib was noted) just had a recent MRI of the brain with and without contrast performed and it showed only stable metastatic deposits compared to one year before and CT of the lungs, thorax and abdomen showed stable right upper lung peribronchial, post-treatment features without plural effusion, and thus no evidence of new lung nodules. Also, CT of the abdomen showed no evidence of developing adenopathy and no bone or soft tissue lesions.

She was thinking about stopping mifepristone since there has been no new growth or new lesions for so many years fearful with the overturn of Roe *vs*. Wade that the drug may prove hard to get. We explained to her that a patient who started mifepristone at the same time as she did who had metastatic fibroblastic osteosarcoma and was doing very well had the same concerns (95). He lived 1,000 miles from our office. His oncologist told him to stop the mifepristone and switch to ifosfamide drip.

Table I. *Drug options for lung cancer other than platinum-based chemotherapy or bevacizumab.*

Targeted mutations	Type of drug	Names of drug
Non-small cell lung cancer		
EGFR	TKI	Afatinib
		Alectinib
		Brigatinib
		Cabozantinib
		Capmatinib
		Ceritinib
		Crizotinib
		Dabrafenib
		Dacomitinib
		Entrectinib
		Erlotinib
		Gefitinib
		Larotrectinib
		Lorlatinib
		Osimertinib
		Pralsetinib
		Selpercatinib
		Tepotinib
		Trametinib
PD-1	Check-point inhibitor	Durvalumab
		Nivolumab
		Pembrolizumab
		Tislelizumab
PD-L1	Check-point inhibitor	Atezolizumab
CTLA-4	Check-point inhibitor	Ipilimumab
		Tremelimumab
ALK	ALK TKI's	Alectinib
		Brigatinib
		Lorlatinib
ROS1	TKI	Cribotinib
		Entrectinib
		Lorlatinib
KRAS	KRAS inhibitor TKI	Sotorasib
METex14	TKI	Capmatinib
		Crizotinib
		Tepotinib
RET		Cabozantinib
		Pralsetinib
		Selpercatinib
BRAF	TKI	Dabrafenib
		Trametinib
PIBF	Membrane progesterone receptor	Mifepristone
Small cell lung cancer		
PD-1	Check-point inhibitor	Camrelizumab
		Nivolumab
		Pembrolizumab
Neo-vascularization	Anti-angiogenic	Anlotinib
Rapid proliferating cells	Alkylating agent	Lurbinectedin

He did not consult our group for our opinion. His wife, a nurse, strongly advised him not to stop the mifepristone. The oncologist opinion was that they would not be able to evaluate the efficacy of this other drug if they were both taken at the same time and there may be drug interactions. They could always restart the mifepristone if the cancer progressed. It did in fact progress rapidly and he died within 5 weeks of stopping mifepristone. We reiterated that PR antagonists seem to stop tumor aggressiveness, and cancers do not seem to find a way to mutate to become resistant to them, but it does not "cure" the cancer and it must be taken without stopping for the rest of the patient's life. If mifepristone is no longer available, we advised her we would switch to ulipristal.

As mentioned, check-point inhibitors do not work well in patients with the *EGFR* driver mutation. In contrast we determined that mifepristone does work well in patients with the *EGFR* mutations when it finally progresses despite osimertinib treatment (43). To date we have not treated patients with any other driver mutations with a PR antagonist. It would be interesting to determine if certain driver mutations make PR antagonist therapy less effective.

Conclusion

With the exception of mifepristone, most countries, including the United States, allow off-label use of medications. If anecdotal case reports also show convincing improvements in length and quality of life, in cases treated with ulipristal in the United States, and possibly telapristone in Europe or Asia, the respective drug manufacturer can present their case for these countries to provide third party financial coverage for these drugs, which would be far less costly than most medical oncologic treatments presently available. For patients with advanced lung cancer and no other treatment options, other than hospice, it seems regrettable not to offer them a PR antagonist off-label option rather than awaiting future studies hopefully leading to the approval of PR antagonists for treating lung cancer.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this manuscript.

Authors' Contributions

The majority of the manuscript was written by the lead author, Jerome H. Check. Trina Poretta is the clinical oncologist who provided the clinical care for some of the patients in this study, but also made contributions especially to the standard therapeutic options for lung cancer. Diane Check was the project manager for the FDA approved study on NSCLC and helped in writing the case reports of the 5 anecdotal cases. She also helped make revisions to the entire manuscript before submission. Maya Srivastava also reviewed the entire manuscript and contributed, especially to the discussion of immunologic treatments for lung cancer.

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