Masonic Cancer Center
University of Minnesota

Phase II Trial of Exemestane in Previously Treated Post-Menopausal Women with Advanced Non-Small Cell Lung Cancer

CPRC# 2015LS095
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Revision History

Version #	Version Date	Summary of Changes	Consent Revision?
	08/18/2015	original to CPRC	n/a
	10/05/2015	In response to CPRC review minor stipulations: • Section 6.3 – patients experiencing a Grade 4 treatment related toxicity will be permanently discontinued from exemestane therapy; • Synopsis, Sections 1.2, 8, 9, 12.2 and Appendix VI – add completion of the quality of life questionnaire (PROMIS-29 Profile) before beginning exemestane, every 3 weeks while on study drug, and at the final treatment visit. • Section 13.3 – expand description of biomarker analysis and indicate they will not be a surrogate Additional changes: • Synopsis, Section 4.1.2 and Eligibility Checklist –Require archived tumor tissue to be available at study enrollment for research related analysis • Clarify enrollment will be 56 patients over 2 years	n/a
	01/07/2016	Initial version to the IRB • Add Pfizer related information regarding drug ordering (section 7) and SAE reporting (section 10.3) • Other minor clarifications through-out	
	02/29/2016	In response AURPAC stipulations (interim version – not submitted to IRB) • Sections 6.2 and 9.1 – change Dexa scan to every 12 months while receiving exemestane (previously every 3 months)	yes
	04/05/2016	In response to IRB and AURPAC stips (incorporates 2/29/2016 version provided to AURPAC only) Two minor updates to the protocol: • Section 4.1.2 - change the number of unstained pathology slides from archived tumor tissue required for eligibility from 3 to 5 • Section 9.1 – research related blood collection: replace a 10 ml red top tube with a 10 ml Cell-Free DNA BCT tube	yes
1	05/26/2016	Eligibility criteria – Synopsis, Sections 3 and 4 – simplify eligibility criteria • make less restrictive by removing upper limit of previous treatments permitted (previously limited to no more than 3 prior treatments) and simplify text in Section 4.1.3 by deleting definitions of treatment types (adjuvant vs maintenance etc.); • lower required hemoglobin count to 8 g/dL (from 9) at enrollment as exemestane does not affect blood counts; • simplify time from previous treatment requirements Synopsis, Sections 4.2.2 and 6.2 - delete exclusion of women diagnosed with osteoporosis; add in Section 6.4 that women with osteoporosis should be on treatment with calcium/vitamin D and/or bisphosphonates Section 9 – Schedule of Activities • add row for disease re-assessment (previously missing) • add an X to the CT of chest/abd/pelvis box under every 6 weeks for disease re-assessment, add a comment no need to repeat at final study visit if done in previous 6 weeks other clarifications and edits including: Section 1.2 add follow-up for survival is for up to 1 year Section 9 - add a row to monitor for stopping rules; require DEXA at baseline only if not done in previous 12 months; change blood	yes

Version #	Version Date	Summary of Changes	Consent Revision?
		volumes for research tubes but total volume unchanged, delete the cycle 12 research sample Section 9. 2 – add a statement regarding testing of tumor tissue Section 13.1 – edit follow-up for response and survival as 12 months from enrollment not through 12 months post-treatment to match rest of protocol Appendix I – update to reflect changes to Section 4	
2	04/17/2018	• Update protocol through-out to enroll post-menopausal women who are progressing on FDA approved immune checkpoint blockade (e.g. pembrolizumab, atezolizumab, or nivolumab) with exemestane being an add on therapy • Updated protocol to current template language	yes
3	09/05/2019	• Sections 4.1 and 9.1 – remove PT/INR criteria as prolonged INR or PTT due to anticoagulation should not be exclusionary • Sections 6.2. and 9 - Remove references to every 2 week nivolumab as now may be given less frequently per current package insert • Update to current template including deleting eligibility checklist as Appendix I and renumbering all appendices, and other edits • Update for future MNCCTN participation	yes
4	02/21/2020	• Section 4.1.1 – - Patients with EGFR/ALK/ROS1 rearrangements should have received an FDA-approved TKI prior to enrollment on this trial • Section 6.1.1 Exemestane Expected Toxicity – change risk section to table format based on NCI risk formatting – change common risk from 10% to 20% of patients potentially experiencing, reword and reorganize some of the risks, add possible liver damage, allergic reaction, and vaginal bleeding under rare occurrence and hair thinning or changes under occasional • Section 6.4 – Duration of Treatment – permit up to a 6 week break from exemestane Section 9.1 – currently up to 3 weeks • Section 9.1 – Add footnote #4 in the table, clarify that questionnaire completion, like research blood collection is tied to the clinical calendar. • Update the term Primary Clinical Research Coordinator to the more general term Study Coordinator	yes
5	07/17/2020	Revert back to the September 2019 risk profile (current IRB approved protocol) with updated risks based on Micromedex: Section 2.3 – state Micromedex is the source of the toxicity profile Section 6.1.1 – revert back to the September 2019 version with new risks tracked (gastric ulcer, cholestatic hepatitis, hair loss or thinning, increased alk phos	yes

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Abbreviations

AI	aromatase inhibitor
BMD	bone mineral density
CPRC	Cancer Protocol Review Committee
CNS	central nervous system
CR	complete response
CTO	Clinical Trials Office
ECOG	Eastern Cooperative Oncology Group
e-CRF	electronic case report form
ER	estrogen receptor
FDA	Food and Drug Administration
ICB	immune checkpoint blockade
IRB	Institutional Review Board
MCC	Masonic Cancer Center
MDSC	myeloid derived suppressor cells
MNCCTN	Minnesota Cancer Clinical Trials Network
NSCLC	non-small cell lung cancer
OnCore	Online Enterprise Research Management Environment
OS	overall survival
PD	progressive disease
PFS	progression free survival
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SOC	standard of care

Synopsis

Phase II Trial of Exemestane in Previously Treated Post-Menopausal Women with Advanced Non-Small Cell Lung Cancer

Study Design: This is a phase II therapeutic study of adding exemestane therapy in post-menopausal women with advanced non-small cell lung cancer (NSCLC) who are progressing while on treatment with an immune checkpoint blockade antibody (pembrolizumab, atezolizumab, or nivolumab).

Enrollment will use a two-stage design. Stage 1 will enroll 10 patients. If at least 2 objective responses are observed at the first disease re-evaluation after beginning oral exemestane, Stage 2 will be activated. In Stage 2, an additional 19 patients will be enrolled for a total of 29 patients. If 4 or more objective responses are observed in the 29 patients, exemestane will be deemed worthy of further investigation in this population.

Primary Objective: To determine a preliminary estimate of response of daily oral exemestane for the treatment of previously treated, advanced non-small cell lung cancer (NSCLC) in post-menopausal women receiving and progressing on immune checkpoint blockade (ICB) therapy.

Secondary Objectives:

- To determine the toxicity profile of daily exemestane in combination with immune checkpoint blockade therapy in this patient population.
- To estimate the disease control rate, progression-free survival (PFS), and overall survival (OS) of exemestane in this patient population through 1 year from study enrollment.
- To estimate quality of life during treatment and for 1 month after discontinuation.

Correlative Objectives:

- To conduct an exploratory biomarker correlative study of clinical outcome utilizing archived tumor tissue and serum collected at baseline and serially during therapy.
- To examine biomarkers in tissue post-treatment at the time of re-biopsy, if performed.
- To examine serum biomarkers of the peripheral immune response after aromatase inhibition.

Treatment Plan Eligible, consenting patients will take exemestane 25 mg once daily by mouth after a meal for a minimum of 6 weeks (2 treatment courses) while continuing on treatment with an FDA-approved anti-PD1 or anti-PD1 antibody. A disease re-evaluation will be performed at 6 weeks and those experiencing a complete response (CR), partial response (PR) or stable disease (SD) based on the Response Evaluation Criteria in Solid Tumors (RECIST) may continue exemestane daily with standard of care ICB until disease progression, unacceptable side effects, or patient refusal/non-compliance. Patients are seen in clinic every 3 weeks with a disease re-evaluation every 6 weeks.

An end of treatment visit occurs 4 weeks after the last dose of exemestane or the start of a new therapy, whichever is earlier. All patients are followed for response until disease progression or the start of a new treatment, then for survival through 1 year from study enrollment.

Key Inclusion Criteria

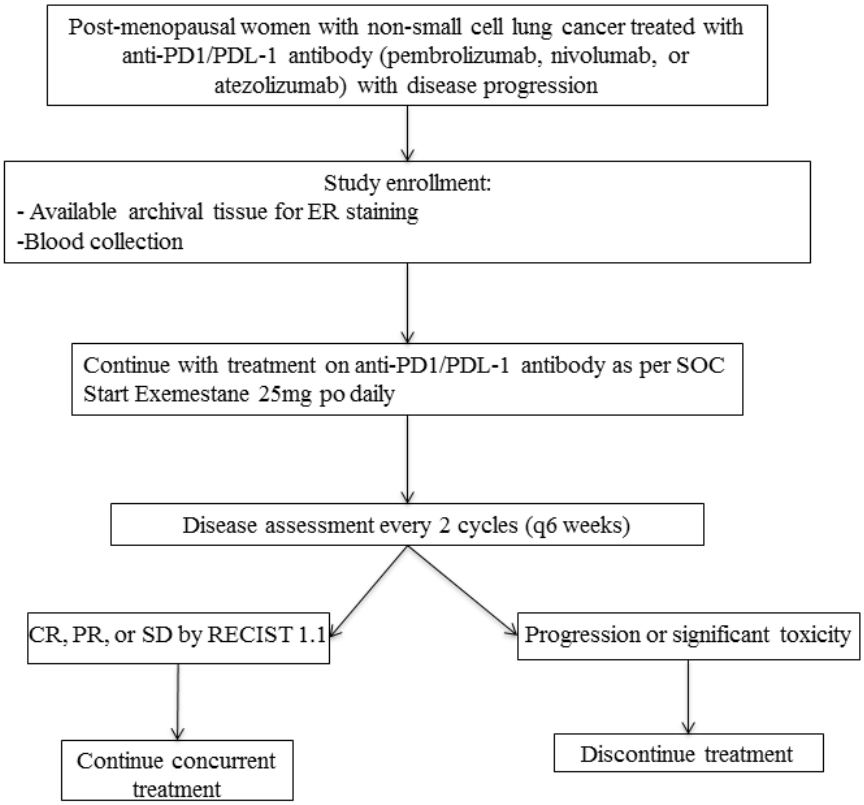
- Advanced stage non-small cell lung cancer (NSCLC) currently receiving an FDA approved anti-PD1 or anti-PDL1 therapy with progressive disease
- Sufficient tumor tissue from the diagnostic or subsequent biopsy either as a block or a minimum of 5 slides for estrogen receptor and aromatase analysis
- Failed at least 1 prior FDA approved treatment regimen for advanced NSCLC - Patients with EGFR/ALK/ROS1 rearrangements should have received an FDA-approved TKI prior to enrollment on this trial.
- Measureable disease per RECIST
- Post-menopausal defined as 1 year or more of amenorrhea and if < 55 years of age estradiol assay < 20 pg/mL
- ECOG performance status 0, 1, or 2

Key Exclusion Criteria

- Untreated or unstable CNS disease
- Inability or unwillingness to swallow tablets
- Currently using hormone replacement therapy (oral or patch) or/and phytoestrogen supplements (i.e. black cohosh)

Enrollment: Stage 1: 10 patients, Stage 2 if activated, 19 additional patients

Treatment Schema



* or unacceptable toxicity, patient refusal/noncompliance/> 3 week break from therapy, or, in the opinion of the treating physician stopping therapy is in the best interest of the patient

- Clinic visit every 3 weeks during treatment
- Maintain SOC ICB specific dosing schedule
- Disease reassessment every 6 weeks during exemestane treatment
- Follow for disease response until disease progression or start of a new therapy, then survival only for 1 year from study enrollment

Patients who are discontinued from standard of care ICB therapy due to toxicity may continue exemestane as single agent provided disease response criteria is met.

1 Objectives

1.1 Primary Objective

The primary objective is to determine a preliminary estimate of response of daily oral exemestane for the treatment of previously treated, advanced non-small cell lung cancer (NSCLC) in post-menopausal women receiving and progressing on immune checkpoint blockade (ICB) therapy.

1.2 Secondary Objectives

- To determine the toxicity profile of daily exemestane in combination with immune checkpoint blockade therapy in this patient population.
- To estimate the disease control rate, progression-free survival (PFS), and overall survival (OS) of exemestane for up to 1 year from study enrollment in post-menopausal women with previously treated advanced NSCLC.
- To estimate quality of life during study treatment and for one month following discontinuation of study treatment.

1.3 Correlative Objectives

- To conduct an exploratory biomarker correlative study of clinical outcome utilizing archival tumor tissue and serum collected at baseline and serially during therapy
- To examine biomarkers in tissue post-treatment at the time of re-biopsy, if performed
- To examine serum biomarkers of the peripheral immune response after aromatase inhibition

2 Background and Rationale

2.1 Advanced Non-Small Cell Lung Cancer

The standard of care for first-line treatment of advanced non-small cell lung cancer (NSCLC) includes platinum based-doublets, such as combinations of cisplatin or carboplatin with either paclitaxel, docetaxel, and vinorelbine or gemcitabine. In patients with advanced NSCLC and good performance status, these doublets lead to predictable response rates of approximately 30%, median survival of 8-9 months and 1-year survival of 30-40%[1]. Alternatives to chemotherapy are also now approved for first line therapy of NSCLC based on molecular biomarkers. Patients whose tumors harbor genetic mutations in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), or ROS1 have superior response rates, progression free survival and overall survival when treated with a targeted oral tyrosine kinase inhibitor. Moreover, patients

whose tumors have >50% expression of programmed death ligand (PDL-1), a marker of immune activation within the tumor microenvironment, have improved outcomes when treated with an immune checkpoint antibody, pembrolizumab.

FDA approved agents for the second and third line therapy of NSCLC includes docetaxel, pemetrexed, and erlotinib[2]. These include two chemotherapeutic agents that are currently approved and in use for second line therapy: docetaxel (75 mg/m^2) (response rates of 6.7% - 8.8%; Median survival of 5.7 months to 7.9 months and 1 year survivals of about 30%); and pemetrexed (response rate of 9.1%, median survival of 8.3 months and 1 year survival of 29.7%)[3-5]. In several randomized controlled trials, immune checkpoint antibodies, have now been approved in the 2nd or 3rd line setting based on improved overall survival compared to docetaxel. Thus, pembrolizumab, nivolumab, and atezolizumab are now commonly used 2nd line agents for the treatment of NSCLC. The major advance of immune checkpoint blockade is that in patients who respond, the duration of response is quite long and some patients (~15%) remain in remission for several years after the initiation of treatment. Unfortunately, the objective response rate remains relatively low in the range of 20-30%. Thus, the majority of patients will not respond to such therapy. While modest improvements have been made in survival and quality of life in patients with advanced NSCLC there is a need to explore new agents with novel mechanisms of action in this patient population. Moreover, novel combination therapies with immune checkpoint blockade are actively sought to improve upon the low response rates with this therapy.

2.2 Therapeutic Potential of Targeting the Estrogen Receptor Pathway in NSCLC

Over the last decade, increasing evidence from multiple disciplines have demonstrated that the estrogen signaling pathway plays an important role in lung tumorigenesis[6] Furthermore, recent data has suggested that anti-estrogen therapy may be an effective therapeutic strategy for advanced stage non-small cell lung cancer (NSCLC)[6,7]. Several large cohort studies have implicated the estrogen receptor pathway in lung tumorigenesis[8,9] and have demonstrated a protective effect of anti-estrogen therapy in the prevention of NSCLC[9,10]. Furthermore, *in vitro* and *in vivo* studies have shown estrogen can modulate expression of genes that are important for cell proliferation in NSCLC[11]. We and others have previously demonstrated that estrogen receptor beta (ERβ) is expressed in the vast majority of NSCLC, including in post-menopausal women[6,12]. This is in contrast to the predominant expression of ER alpha (ERα) protein in breast cancer[12]. Furthermore, the aromatase enzyme is expressed in 86% of NSCLC and high expression of aromatase is a poor prognostic marker in post-menopausal women with NSCLC[13]. Over the last decade, increasing

evidence from multiple disciplines has demonstrated that the estrogen signaling pathway plays an important role in lung tumorigenesis[14,15]. Recent data has suggested that anti-estrogen therapy may be an effective therapeutic strategy for advanced stage non-small cell lung cancer (NSCLC)[16-18].

Preclinical and early clinical studies on anti-estrogen therapy appear promising. Aromatase inhibitors (AI) suppressed cell proliferation *in vitro* as well as in lung tumor xenografts[13]. Furthermore, treatment with an AI significantly inhibited lung tumor formation in a carcinogen induced model of lung cancer[15]. In addition, we have previously demonstrated that significant crosstalk exists between the estrogen and EGFR signaling pathways[16]. We have validated this preclinical observation in a recent phase II clinical trial, combining fulvestrant and erlotinib, an EGFR tyrosine kinase inhibitor, which demonstrated that the combination was well-tolerated and had a significant clinical benefit rate in patients with *EGFR* wild type tumors[18]. Recent data suggest that hormonal therapy can have significant impact upon the immune microenvironment of tumors[19]. Oopherectomy of female mice improved the survival of mice bearing lung cancer in a syngeneic mouse model. Likewise, estrogen supplementation led to enhanced tumor growth. This effect was associated with increased myeloid derived suppressor cells (MDSC) in the tumor microenvironment which was reversed upon oophorectomy. These effects were tumor independent as knockout of ER on hematopoietic cells resulted in improved survival of tumor bearing mice and resulted in reduced MDSCs and enhanced CD8 and CD4+ T cells in the tumor microenvironment. Finally, in human squamous cell NSCLC, the expression of PDL-1 is highly correlated to ER expression providing a further link between ER signaling and immune regulation in the tumor microenvironment (unpublished data).

Estrogen Receptors are also expressed by T cells[20,21], myeloid-derived suppressor cells (MDSC)[22] and macrophages[23]. E2 promotes human epidermal growth factor receptors (HERs) ligand release, including amphiregulin (AREG), and AREG has been shown to suppress T cell response and promote T regulatory function[24]. Both macrophages and T cells express EGFR receptor that promotes their tumorigenic phenotypes (5). A recent report suggests that E2 increases the mobilization of pro-tumor immune cells and promotes an immunosuppressive tumor microenvironment (TME)[25].

Our recent unpublished data also show that E2 at 10nM induces PD-L1 expression in two NSCLC cell lines (201T, A549) (Figure 1), suggesting that an aromatase inhibitor could reverse immunosuppression mediated through PD-L1.

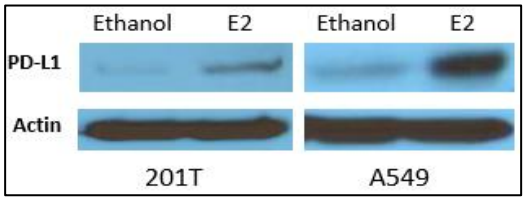


Figure 1: Immunoblots of whole cell lysates from two NSCLC cell lines treated with E2 at 10nM or ethanol as a vehicle for 24 hr. 30µg of each sample were analyzed by western blotting using rabbit monoclonal anti-PD-L1 antibody and rabbit β-actin antibody.

These observations suggest that E2 can suppress T cells cytotoxic activity against lung cancer cells, stimulate M2 macrophages, increase activity of myeloid derived suppressor cells, and enhance activity of Treg cells (shown in Figure 2), as well as stimulate NSCLC cells directly. Since exemestane will reduce E2 levels in the tumor microenvironment, immunosuppression should be reversed, and adding exemestane to an immune checkpoint blocker should be beneficial.

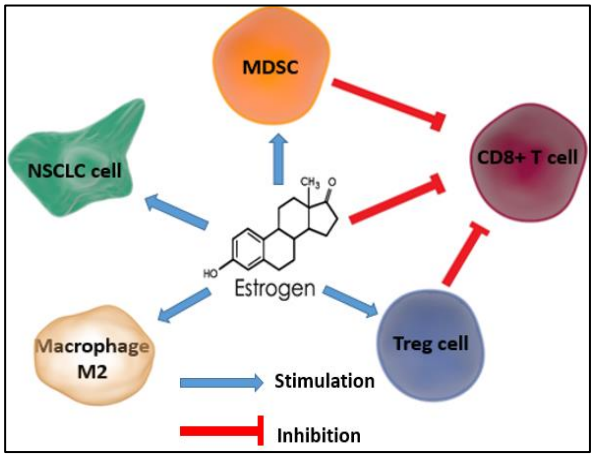


Figure 2*:* Summary of the expected immunosuppressive effects of E2. E2 will enhance the activation of MDSC leading to more suppression of T cell cytotoxic activity. E2 will also promote the conversion of T cell to Treg state. Macrophages will be polarized toward M2 phenotype with less phagocytic activity. Lastly, E2 will enhance NSCLC proliferation and immune-escape through upregulation of PD-L1 expression.

Given these promising preclinical and clinical studies, it is imperative to evaluate anti- estrogen therapy in NSCLC.

Based on work in breast cancer, aromatase inhibitors are very effective in blocking estrogen-driven pro-cancer effects by inhibit production of the hormone estrogen, and have shown superior efficacy against breast cancer progression than agents such as tamoxifen or fulvestrant that block the estrogen receptor[26]. Aromatase

inhibitors (AIs) have a good safety profile and have been given to post-menopausal women for up to 5 years[27]. AIs are contraindicated in men due to a buildup of testosterone when aromatase is inhibited[28]. AIs are administered orally on a daily regimen, while fulvestrant is only available as a depot IM injection. We are proposing to use the AI exemestane in the female post-menopausal population with advanced lung cancer that has failed prior chemotherapy.

2.3 Exemestane

Exemestane (AROMASIN®) is an aromatase inhibitor initially approved by the FDA in 1999 for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy. On October 5, 2005 it was approved by the FDA for the adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy. Standard approved dosing is 25 mg PO per day continuously.

Safety and efficacy were evaluated in the Intergroup Exemestane Study (IES), a double-blind, multicenter, international clinical trial in postmenopausal women with early stage breast cancer who had received two to three years of adjuvant tamoxifen. Four thousand seven hundred and twenty four patients in the intention-to-treat population were randomized to either continue tamoxifen (20-30 mg/day) or switch to exemestane (25 mg/day) to complete a total of five years of adjuvant hormonal therapy. In the hormone receptor-positive subpopulation representing about 85 percent of the trial patients, disease free survival (DFS) was significantly improved (HR=0.65, 95 percent CI: 0.53-0.79, p=0.00001) in the exemestane arm compared to the tamoxifen arm.

Adverse Reactions: Early breast cancer: Adverse events occurring in ≥10% of patients in any treatment group (AROMASIN vs. tamoxifen) were hot flushes (21.2% vs. 19.9%), fatigue (16.1% vs. 14.7%), arthralgia (14.6% vs. 8.6%), headache (13.1% vs. 10.8%), insomnia (12.4% vs. 8.9%), and increased sweating (11.8% vs. 10.4%). Discontinuation rates due to AEs were similar between AROMASIN and tamoxifen (6.3% vs. 5.1%). Incidences of cardiac ischemic events (myocardial infarction, angina, and myocardial ischemia) were AROMASIN 1.6%, tamoxifen 0.6%. Incidence of cardiac failure: AROMASIN 0.4%, tamoxifen 0.3%.

Advanced breast cancer: Most common adverse events were mild to moderate and included hot flushes (13% vs. 5%), nausea (9% vs. 5%), fatigue (8% vs. 10%), increased sweating (4% vs. 8%), and increased appetite (3% vs. 6%) for AROMASIN and megestrol acetate, respectively.

As this study is directed at post-menopausal women with advanced lung cancer, IBM Micromedex® available through the University of Minnesota Libraries is being used as the source of risks in this protocol assessed on July 17, 2020. This closely aligns to the toxicity profile found in the September 2019 protocol version with a few updates.

Refer to the AROMASIN prescribing information for additional information at http://www.pfizer.com/products/product-detail/aromasin.

2.4 Anti-PD-1/Anti-PDL-1 Therapy for NSCLC

There are currently 3 FDA-approved antibodies for the treatment of metastatic NSCLC in the 2nd or 3rd line setting, pembrolizumab, nivolumab, and atezolizumab. These are all based on randomized controlled trials showing an improved progression free survival and overall survival comparing immune checkpoint blockade to docetaxel chemotherapy[29]. Across all of the trials, the objective response rate to immune checkpoint blockade is approximately 20-30% in unselected patients. In each of these trials the response rate was improved in patients whose tumors expressed a high level of PDL-1 on the cell surface. In previously untreated patients with PDL-1 expression on >50% of tumor cells, the response rate to pembrolizumab was improved to 55% and PFS and OS were improved compared to standard first-line chemotherapy in the Keynote-024 trial leading to FDA approval of pembrolizumab in the first line setting for NSCLC[30]. Thus at this time, the majority of patients are being treated with immune therapy at some point in their treatment course. While immune checkpoint blockade response can be quite durable, the vast majority of patients with a response will ultimately become resistant to therapy or be primarily resistant. Thus, novel strategies to overcome resistance are needed.

2.5 Rationale

While modest improvements have been made in survival and quality of life in patients with advanced non-small cell lung cancer (NSCLC) there is a need to explore new agents and combinations with novel mechanisms of action in an effort to improve clinical outcomes in this patient population. With the introduction of immune checkpoint blockade and the durability of response, the vast majority of patients with NSCLC are receiving immune checkpoint blockade at some point in there therapy. However, response rate is relatively low spawning interest in developing novel combination therapies that can improve upon the response or generate responses in patients who are failing therapy. It is generally accepted that the aromatase inhibitor (AI) exemestane is less toxic then chemotherapy, yet potentially it can provide equal or greater benefit. In hormone receptor positive breast cancer, anti-estrogen therapy is a first-line treatment for metastatic disease,

and is given as adjuvant therapy for 5 years in earlier stage disease. Exemestane has been used in tens of thousands of women and its efficacy and side effect profile has been well established. Furthermore, preclinical and clinical data suggest that there might be a role of estrogen receptor signaling in maintaining immune suppression in the tumor microenvironment. Therefore, we propose a 2-stage phase II trial of exemestane in previously treated postmenopausal women with metastatic NSCLC who are progressing on anti-PD1 or anti-PDL1 therapy to determine if aromatase inhibition will result in treatment responses in this patient population and to determine whether ER-related biomarkers can identify patients likely to receive clinical benefit.

The estrogen pathway inhibition is a promising novel target in NSCLC. Preclinical evidence support targeting the synthesis of estrogen in NSCLC as a strategy that may result in enhanced antitumor activity.

3 Study Design

This is a phase II study of daily oral exemestane for the treatment of advanced non-small cell lung cancer in post-menopausal women who are progressing on an FDA approved immune checkpoint blockade therapy. The study will be conducted using Simon's two-stage design. [30] Stage 1 will enroll 10 patients. If at least 2 objective responses are observed at the first disease re-evaluation at 6 weeks after beginning oral exemestane, Stage 2 will be activated. In Stage 2, an additional 19 patients will be enrolled for a total of 29 patients. If 4 or more objective responses are observed in the 29 patients, exemestane will be deemed worthy of further investigation in this patient population.

4 Patient Selection

Study entry is open to post-menopausal women regardless of race or ethnic background. While there will be every effort to seek out and include minority women, the patient population is expected to be similar to that of advanced non-small cell cancer lung studies at the University Of Minnesota. Men are not eligible for this study as exemestane works by suppressing estrogen production. Women of child-bearing potential are not eligible as exemestane is FDA pregnancy category X – known harm to the unborn.

4.1 Inclusion Criteria

4.1.1 Recurrent or progressive advanced stage non-small cell lung cancer (no small cell component) with most recent treatment being an FDA approved immune checkpoint inhibitor (pembrolizumab, atezolizumab, or nivolumab)

NOTE: Pathology reports documenting the diagnosis of NSCLC are required to be reviewed to confirm outside diagnosis

4.1.2 Sufficient tumor tissue available from original diagnosis or subsequent biopsy for analysis of estrogen receptor and aromatase – tumor block or a minimum of 5 unstained slides

4.1.3 Failed at least 1 prior FDA approved treatment for advanced NSCLC. Patients with EGFR/ALK/ROS1 rearrangements should have received an FDA-approved TKI prior to enrollment on this trial.

4.1.4 Measureable disease by RECIST version 1.1 (Appendix II)

4.1.5 Post-menopausal defined as

- Age ≥ 55 years and 1 year or more of amenorrhea
- Age < 55 years and 1 year or more of amenorrhea with an estradiol assay < 20 pg/mL
- Surgical menopause with bilateral oophorectomy

4.1.6 ECOG performance status 0, 1 or 2 (Appendix I)

4.1.7 Life expectancy of 3 months or more in the opinion of the enrolling investigator and documented in the medical record

4.1.8 Adequate organ function within 14 days of study enrollment defined as:

Hematology:

Absolute neutrophil count (ANC) $\geq$ 1500/mm^3, Platelets $\geq$ 100,000/mm^3, Hemoglobin ≥ 8 g/dL

Biochemistry:

Total Bilirubin within normal institutional limits

AST/SGOT and ALT/SGPT ≤ 2.5 x upper limit of normal (ULN), except if there is known hepatic metastasis, wherein transaminases may be ≤ 5 x institutional ULN.

Serum creatinine ≤ 1.5 mg/dl or glomerular filtration rate > 50 ml/min

4.1.9 Must have recovered to CTCAE v 4 Grade 1 or better from the acute effects of any prior surgery, chemotherapy or radiation therapy. Chronic residual toxicity (i.e. peripheral neuropathy) is permitted

4.1.10 A minimum time period must elapse between the end of a previous treatment and start of study therapy:

- 1 week from the completion of radiation therapy for brain metastases
- 4 weeks from the completion of chemotherapy or any experimental therapy
- 4 weeks from prior major surgery (such as open biopsy or significant traumatic injury)

4.1.11 Voluntary written consent before any research related procedures or therapy

4.2 Exclusion Criteria

4.2.1 Known active CNS disease - If patient has history of brain metastases, the brain lesions must have been treated with radiation and/or surgery - patients should be neurologically stable and requiring ≤10mg oral prednisone equivalence of steroids per day

4.2.2 Any toxicity from immune-related toxicity from prior immune therapy that would preclude further treatment with anti-PD-1/PDL-1 inhibitor or ongoing IR toxicity ≥ Grade 2

4.2.3 Requiring > 10 mg prednisone equivalence of steroids per day for immune-related toxicity

4.2.4 Inability or unwilling to swallow study drug

4.2.5 Any gastrointestinal condition causing malabsorption or obstruction (eg, celiac sprue, gastric bypass surgery, strictures, adhesions, history of small bowel resection, blind loop syndrome)

4.2.6 Currently using hormone replacement therapy (oral or patch) or/and phytoestrogen supplements (i.e. black cohosh)

4.2.7 Known hypersensitivity to exemestane or its excipients

4.2.8 Any serious underlying medical condition that, in the opinion of the enrolling physician, would impair the ability of the patient to receive protocol treatment

4.2.9 Prior malignancy, with the exception of curatively treated squamous cell or basal carcinoma of the skin or in situ cervical cancer, unless there is a 3-year disease-free interval

4.2.10 Concomitant use of strong CYP3A4 inducers such as rifampicin, phenytoin, carbamazepine, phenobarbital, or St. John’s wort as these may significantly reduce the availability of exemestane

5 Patient Registration and Study Enrollment

Written consent must be obtained prior to the performance of any research related tests or procedures. Consent is usually obtained before final eligibility is determined.

5.1 Registration with the Masonic Cancer Center Clinical Trials Office

Any patient who has been consented is to be registered in OnCore by the Study Coordinator or designee. If a patient is consented, but not enrolled, the patient's record is updated in OnCore as a screen failure and reason for exclusion recorded.

5.2 Study Enrollment with the Masonic Cancer Center Clinical Trials Office

To be eligible for study enrollment, the patient must sign the treatment consent and meet each of the inclusion criteria and none of the exclusion on the eligibility checklist based on the eligibility assessment documented in the patient's medical record.

The Study Coordinator or designee will assign the study treatment arm to complete enrollment.

5.3 Patients Who Are Enrolled and Do Not Receive Study Treatment

If a patient is enrolled in the study and is later found not able to begin exemestane, for whatever reason, the patient will be removed from study and treated at the physician's discretion. The PCRC or designee will update OnCore of the patient's non-treatment status. The reason for removal from study prior to starting study treatment will be clearly indicated in OnCore. The patient will be replaced to complete enrollment.

6 Treatment Plan

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy. Refer to Section 6.3 for prohibited medications during exemestane therapy.

6.1 Exemestane Dosing Plan

Exemestane is self-administered as a single, 25 mg tablet by mouth following a meal once daily at approximately the same time each day. If the dose is missed by more than 8 hours, the patient will skip that dose and take the next scheduled dose at the usual time.

Exemestane will continue once daily until disease progression, unacceptable side effects, patient refusal/non-compliance, or the treating physician feels discontinuing therapy is in the best interest of the patient.

The patient will be provided with a daily drug log to record the time of administration, side effects, and any missed doses. The patient will be instructed to bring the drug log and study drug bottles (including any empties) to each appointment for reconcilement.

During the first treatment cycle only, the patient will be contacted by a member of the research staff 8 to 12 days after dosing was started to inquire “how things are going” and to see if she has any questions or concerns.

For the purpose of this study each 3 week (21 day) dosing period will be considered a treatment course. A disease re-assessment will be done after every 2 treatment courses.

Participants who do not undergo the 1st disease re-evaluation will be considered unevaluable and replaced.

6.1.1 Exemestane Expected Toxicity

Based on extensive use in post-menopausal women with breast cancer as sourced through IBM Micromedex® available through the University of Minnesota Libraries:

In general, exemestane is well tolerated at this dose when given long term to post-menopausal women with breast cancer. It is thought that adding exemestane to ongoing immune checkpoint blockade the risks profile for neither drug will be different.

Rare, but potentially serious side effects

Bone loss. Exemestane lowers the level of estrogen in the body and may reduce bone mineral density (BMD) over time, possibly increasing the risk of bone fracture. A DEXA scan will be done at baseline, if none performed in the previous 12 months and every 12 months while receiving exemestane.

Chest pain, heart failure, or stroke. A small number of women had chest pain, heart failure, or a stroke while taking exemestane

Occurring in less than 1 out of 100 women
Gastric ulcer
Cholestatic hepatitis, hepatitis

Common side effects (occurring in 10 or more out of 100 women)

- hot flashes
- fatigue
- joint pain
- headache
- insomnia
- increased sweating
- depression
- feeling anxious
- upset stomach
- difficulty breathing
- hair loss or thinning
- an increase by a blood test of a liver enzyme (alkaline phosphatase) that may indicate a bone disorder or liver disease

Use of estrogens (such as hormone replacement therapy or HRT) and phytoestrogen supplements (such as black cohosh) to relieve the menopausal like side effects are prohibited during exemestane treatment.

Only post-menopausal women are enrolled in this study as taking exemestane during pregnancy is known to cause birth defects and/or miscarriages.
Refer to the prescribing information for additional details.

We do not expect any difference in the toxicity profile of exemestane when it is added to an ongoing treatment with anti-PD1 or anti-PDL1 antibody treatment. There are ongoing clinical trials in breast cancer using the combination of hormone therapy and an immune checkpoint blockade.

6.1.2 Exemestane Dose Interruptions and Modifications

There are no dose reductions/modifications recommended for exemestane related toxicities; however patients should be treated according to Institutional practices. If a patient experiences a Grade 4 toxicity felt at least possibly related to exemestane, the study drug will be discontinued per Section 6.4. Patients will not make up missed or vomited doses of exemestane.

6.2 Immune Checkpoint Blockade Therapy

All patients will continue treatment with their prior anti-PD1 or anti-PDL1 antibody treatment as per standard of care.

Dose delays or modifications for the ICB agent will be per standard of care and independent of exemestane therapy. A summary of the expected toxicity for each of the three possible ICB agents is provided in Appendix IV.

ICB therapy will be obtained through the same mechanism and will continue to be charged to the patient and her third party payer as before study enrollment.

If the ICB therapy is delayed, exemestane therapy should continue as medically appropriate.

Exemestane may be continued at the discretion of the treating investigator if the ICB therapy is permanently discontinued.

6.3 Supportive Care and Prohibited Medications

Commercially available palliative and supportive care for disease-related symptoms should be offered to all treated patients.

Patients with pre-existing osteoporosis should be on treatment with calcium/vitamin D and/or bisphosphonates.

Patients must be instructed not to take any additional medications (including over-the-counter products) during the study without prior consultation with her study doctor. Use of estrogens (i.e. hormone replacement therapy) and phytoestrogen supplements (i.e. black cohosh) are prohibited during exemestane treatment.

Concomitant use of strong CYP 3A4 inducers decreases exemestane exposure therefore their use will be prohibited. For a list of CYP34A inducers refer to Appendix III.

No chemotherapy, hormonal anticancer therapy, or experimental anticancer medications other than those study related will be permitted while the patient is on study. Any disease progression requiring other forms of specific anti-tumor therapy will be cause for discontinuation from the study.

6.4 Duration of Study Treatment

Treatment continues for a minimum of 2 cycles (6 weeks) and then until disease progression unless one of the following occurs:

- Patient experiences unacceptable side effects exemestane
- Patient refuses further treatment or is non-compliant
- Patient requires other anti-cancer therapy
- A greater than 6 week break from exemestane therapy occurs, regardless of cause
- In the opinion of the treating investigator, continuing on study therapy is not in the best interest of the patient

Exemestane may be continued as a single agent at the discretion treating investigator in the event the ICB therapy is permanently discontinued due to

unacceptable toxicity (refer to Appendix IV for potential risks of ICB therapy) as long as none of the above criteria is not met.

An end of treatment visit occurs 4 weeks (± 1 week) after the last dose of exemestane or prior to the start of a new therapy, whichever is shorter, to assess for ongoing toxicity and for the patient to return their study drug supply and daily drug log.

6.5 Duration of Study Participation

Direct study participation stops with the end of treatment visit; however all patients are followed for 1 year from the start of study treatment or until death, whichever is shorter.

Patients who discontinue treatment due to disease progression are followed for survival only (medical record review, local MD or patient contact) for 1 year from study treatment start.

Patients who discontinue treatment in the absence of disease progression are followed for disease response per standard of care until disease progression or the start of a new treatment, whichever is shorter and then for survival only for 1 year from study treatment start.

By 1 year from treatment start, all patients should have a last known date alive or a death date with cause recorded in OnCore, as well as, an initial date for disease progression in association with exemestane treatment.

7 Exemestane Drug Information

Names: exemestane, AROMASIN®, 6-Methyleneandrosta-1,4-diene-3,17-dione

Category: Aromatase Inhibitors

Indications: 1) For the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy and 2) adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy.

Pharmacology: Aromatase is an enzyme that converts hormones to estrogen in the body's adrenal glands. The aromatase inhibitors (AIs) are drugs that reduce estrogen levels by blocking the action of aromatase in the adrenal glands. The selective AIs (SAIs) selectively reduce levels of estrogen without interfering with levels of other

steroid hormones that are produced by the adrenal gland. Drugs in this class include anastrozole (Arimidex ™), letrozole (Femara ™) and exemestane (Aromasin ™)

Availability: For the purposes of this study a commercial formulation of Aromasin will be provided by the manufacturer, Pfizer. The study specific drug reorder form is attached in OnCore under this study. It is recommended that a drug inventory sufficient to treat study subjects for approximately four (4) weeks be maintained while waiting for additional ordered supplies.

Drug Accountability: The study drug supply will be stored and dispensed by the University of Minnesota Medical Center, Fairview Investigational Drug Services (IDS) Pharmacy. IDS will be responsible for drug accountability through the study. IDS will provide study drug to participating MNCCTN sites.

Dosage and Administration Schedule: One 25 mg tablet once daily after a meal

Dose Forms and Strengths: Aromasin Tablets are round, biconvex, and off-white to slightly gray. Each tablet contains 25 mg of exemestane. The tablets are printed on one side with the number “7663” in black.

Storage and Stability: Store at 25°C (77ºF); excursions permitted to 15°–30°C (59°–86°F).

Drug Return/Destruction: At the end of the study and after final reconciliation, IDS will destroy any remaining drug according to their current SOP.

Expected Side Effects: refer to Section 6.1.1.

FDA Pregnancy Category X

Contraindications and Counseling:
Patients with a known hypersensitivity to the drug or to any of the excipients

Women of premenopausal endocrine status, including pregnant women

Patients should be informed that they should not take estrogen-containing agents while they are taking exemestane as these could interfere with its pharmacologic action.

Patients should be informed that AROMASIN lowers the level of estrogen in the body. This may lead to reduction in bone mineral density (BMD) over time. The lower the BMD, the greater the risk of osteoporosis and fracture.

Refer to the Aromasin Prescribing Information (https://www.pfizer.com/products/product-detail/aromasin) for additional information

8 Measurement of Effect

For the purposes of this study's primary endpoint, patients should be re-evaluated for response every 6 weeks.

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Refer to Appendix II for the complete RECIST guidelines.

Quality of life scores, as measured by PROMIS, will be evaluated descriptively at baseline, every 3 weeks during and at the end of treatment visit using medians, ranges, interquartile ranges and boxplots to look for trends in various areas measured by PROMIS.

9 Schedule of Activities

Note: Study visits are scheduled every 3 weeks independent of the immune checkpoint blockade therapy administration per standard of care. During exemestane a ±2 day window is permitted for every 3 week visits (start of new treatment cycle) and a ±7 day window is permitted for the every 6 week disease reassessment. The end of treatment (EOT) visit 30 days after the last dose of study drug may be performed with a ±7 day window. Follow-up visits are per standard of care with disease status and survival status abstracted from the medical record.

9.1 Schedule of Patient Tests and Procedures

	Baseline (within 14 days of enrollment)	**During Exemestane Therapy**		**End of Treatment Visit** 4 weeks ±1 week) after final dose of exemestane	**Follow-up**	
		Every 3 weeks (± 2 days)	Every 6 weeks (± 1 week)		disease response (until PD or start of new therapy)	survival at 1 year (all patients)
ASSESSMENTS						
Witten consent	X					
Medical history	X	X		X		
Review of prior anti-cancer therapy	X					
Concomitant meds	X	X				
Physical exam	X	X				
Vital Signs	X	X				
Weight	X	X				
ECOG Performance status	X	X				
Disease re-assessment			X		X	
Symptom and toxicity notation (pt diary)	X	X		X		
LABORATORY EVALUATIONS						
CBC/diff, plts	X	X				
Comprehensive Metabolic Profile (CMP)	X	X				
Estradiol assay[2]	X					
SCANS AND PROCEDURES						
CT of chest/abd/pelvis	X[1]		X	X (if not done in previous 6 weeks)	X[4]	
MRI or CT of brain if previous hx of CNS dz or as clinically indicated	X[1]					
DEXA scan	X[1] (perform only if none in previous 12 months)	repeat every 12 months				
CONTINUATION OF STANDARD OF CARE IMMUNE CHECKPOINT INHIBITOR THERAPY						
Nivolumab pembrolizumab, or atezolizumab	Continue per SOC while maintaining every 3 week visits for exemestane					
RESEARCH RELATED						
Exemestane		25 mg po once a day every day				
Research staff "check-in"[3]		Cycle 1 only between Day 8 and 12				
Reconciling of Exemestane tablets		X		X		
Quality of Life Questionnaire (PROMIS–29 Profile)	X	X		X		
Monitoring for stopping rule events		Refer to Section 10.3				
Blood Samples 30 ml serum (red top) 20 ml EDTA (purple top) 20 ml cell-free DNA BCT tube	X	X prior to cycle 2, 3, and 5		X		
Blood Samples 10 mL green top tube for PBMC	X	X prior to Cycle 2 and 3				
biopsy material[5]	X	at the time of biopsy for clinical reasons				

1 Within 4 weeks of study enrollment

2 For women < 55 years of age

3 A member of the research staff will contact the patient to see how things are going (screen for toxicity) and if they have any questions
4 Per standard of care for patients who discontinued exemestane for reasons other than disease progression – abstract results from medical record
5 At enrollment archived from original diagnosis will request 15 unstained slides but require a minimum of 5 unstained slides for eligibility or resection and fresh at any time tissue is obtained for clinical reasons (i.e. SOC) - consent for tissue is embedded in the treatment consent

All research blood samples go to the Masonic Cancer Center's Translational Therapy Lab (TTL).

Research sample collection and questionnaire completion is tied to the clinical care schedule of events and their associated window for performance. Therefore, if a clinical time point does not occur or is altered, the research related time point will be adjusted (or eliminated) as appropriate.

9.2 Research Related Tests and Procedures

The PROMIS-29 Profile (Appendix VI) will be completed before starting exemestane, every 3 weeks while taking the study drug, and at the end of treatment visit.

Correlative studies will examine biomarkers in the Estrogen Receptor (ER) pathway including circulating levels of hormones and products of ER response genes. DNA will be extracted from blood collected at baseline, during treatment, and at progression and sent for sequencing using the Guardant360 assay to determine if mutations are present that are correlated with resistance to an aromatase inhibitor. Three hundred sixty (360) common mutations will be analyzed that have been used to monitor breast cancer patents on aromatase inhibitor therapy. Additionally, since cigarette smoking is associated with increased ER expression[29], we will measure serum cotinine in patients at baseline as a measure of recent tobacco smoke exposure.

Tumor tissue will be analyzed ERβ receptor expression and aromatase at baseline using immunohistochemistry (IHC). Additionally, we will analyze PDL-1 expression if not already done for clinical reasons. Finally, we will evaluate tumor sections for CD8 T cell staining and MDSC on archival tissue as well as any post-treatment tissue obtained.

Finally, peripheral blood mononuclear cells (PBMCs) will be obtained at baseline and prior to Cycle 2 and 3 to evaluate the peripheral immunophenotype prior to and after initiation of exemestane.

10 Adverse Event Monitoring, Recording and Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE).

A copy of the CTCAE can be downloaded from the CTEP home page http://evs.nci.nih.gov/ftp1/CTCAE/About.html

10.1 Definitions

Note: throughout this section the generic term "drug" refers to the exemestane.

The following definitions are based on the Code of Federal Regulations Title 21 Part 312.32 (21CFR312.32(a)).

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Life-Threatening Adverse Event Or Life-Threatening Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death.

Serious Adverse Event Or Serious Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected Event: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in protocol-related documents (e.g. protocol, consent documents, investigator brochure, package insert), or is not

listed at the specificity or severity that has been observed or given the characteristics of the subject population being studied.

Attribution: is the relationship between an adverse event or serious adverse event and the study drug. Attribution is assigned as follows:

- Definite – The AE is clearly related to the study drug
- Probable – the AE is likely related to the study drug
- Possible – the AE may be related to the study drug
- Unlikely – the AE is doubtfully related to the study drug
- Unrelated – the AE is clearly not related to the study drug

Attribution must be assigned by the treating physician or the PI.

The following definitions are from the Masonic Cancer Center's Data and Safety Monitoring Plan (http://z.umn.edu/dmsp)

Major Deviation: A deviation or violation that impacts the risks and benefits of the research; may impact subject safety, affect the integrity of research data and/or affect a subject's willingness to participate in the research. Deviations that place a subject at risk, but do not result in harm are considered to be major deviations.

Minor Deviation: A deviation or violation that does not impact subject safety, compromise the integrity of research data and/or affect a subject's willingness to participate in the research.

10.2 Adverse Event Monitoring and Documentation

10.2.1 Event Monitoring

Monitoring for adverse events will begin with the start of the exemestane and continue through and including 28 calendar days after the last dose of exemestane.

10.2.2 Event Documentation

Adverse events occurring after the initiation of exemestane treatment through and including 28 calendar days after the last dose must be documented. Refer to Section 6.1.1 for a list of expected toxicities of exemestane and Appendix IV for a list of expected toxicities for the ICB therapy.

Since a key outcome parameter of this study is to characterize the toxicities of exemestane in combination with an FDA approved immune checkpoint inhibitor in this patient population, adverse event documentation requirements will be

determined based on grade, expectedness and relationship to study therapy as follows:

	CTCAE Grade 1	CTCAE Grade 2		CTCAE Grade 3		CTCAE Grade 4 and 5
	Expected or Unexpected	**Expected**	**Unexpected**	**Expected**	**Unexpected**	**Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	Not required	Not required	Required	Required
Possible Probable Definite	Not required	Not required	Required	Required	Required	Required

In addition any event meeting the definition of a serious adverse event (SAE) regardless of attribution that occurs during this period will be documented in the source document and recorded in OnCore.

After the end of treatment visit, monitoring for adverse event will become less frequent based on the schedule in Section 9 and only events at least possibly related to study treatment (based on the table above) will be documented upon knowledge.

10.3 Stopping Rule Events

For the purpose of this protocol any Grade 4 or 5 treatment related event and any Grade 3, 4, or 5 immune related adverse event (pneumonitis, colitis, nephritis, myocarditis or hepatitis) will be considered excess toxicity per Section 13.4 and be reported as a stopping rule event using the Event Form found in OnCore.

Events that count toward an early study stopping rule do not necessarily constitute an event requiring expedited reporting and should only be reported as such if they meet the criteria found in Section 10.5.

10.4 SAE and Death Documentation

The reporting period for this study is from initiation of study treatment (exemestane) through and including 28 days after the last dose of exemestane. However, after this time point, the investigator must report upon knowledge any study treatment related meeting the definition of a serious adverse event (SAE) using the MCC SAE Report Form in OnCore.

Deaths, including due to disease, within the follow-up period will be recorded as an SAE. Deaths due to disease should be recorded as a Grade 5 “Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease).

In addition, upon knowledge, the death date and cause must be reported in the patient follow-up tab in OnCore using the comment field in the survival status section to record the cause.

10.5 MNCCTN Required Reporting To the MCC CTO

The following events are to be reported to the Masonic Cancer Center Clinical Trials Office in an expedited manner based on the table below. In addition, the Network site is responsible for reporting to their local IRB as required.

Event Type	Reporting Timeframe	Form in OnCore to Use
Any event meeting the definition of serious and all patient deaths	Within 24 hours of knowledge	SAE Report Form
Stopping Rule Events	Within 24 hours of knowledge	Stopping Rule Event Form
Major Deviations, as defined in Section 10.1.	Within 5 working days of knowledge	Deviation Report Form

The MCC CTO is responsible for reporting qualifying events to the UMN IRB, Pfizer and the MMC SAE coordinator per Section 10.6.

10.6 Required Reporting By the CTO to UMN IRB, Pfizer, and MCC SAE Coordinator

Agency reporting to	Criteria for reporting	Timeframe	Form to Use	Submission address/ fax numbers
U of MN IRB	Unexpected Death, Information that indicates a new or increased risk, or a safety issue.	5 Business Days	Ethos Reportable New Information (RNI)	Via Ethos and/or Oncore
	Deviations that occur at MCC	5 Business Days	OnCore Deviation Form and Ethos RNI	
Pfizer	Abstracted from Pfizer's Safety Reporting Reference Manual for Investigator-Initiated Research (IIR) Interventional Studies Using the criteria for Mature Anti-Cancer Products- SAEs are reported only if they are: • Deaths that occur during the study reporting period • SAE's that occur during the study period and are assessed by the investigator as both related to exemestane and unexpected • Any related SAE that occur after the study reporting period that the investigator becomes aware of Refer to the Safety Reporting Manual found as an attachment under this study in OnCore	immediately upon awareness, if the SAE is fatal or life-threatening – regardless of the extent of available information **or** within 24 hours of first awareness of the SAE, if the SAE is not fatal or life-threatening	Attached in OnCore under this study	Refer to Reportable Event Fax Cover Sheet – attached in OnCore under this study
Masonic Cancer Center SAE Coordinator	Events that meet the criteria of an early study stopping rule	At time of reporting	Event Form	SAE Coordinator mcc-saes@umn.edu

11 Study Data Collection and Monitoring

11.1 Data Management

This study will collect regulatory and clinical data using University of Minnesota CTSI's instance of OnCore® (Online Enterprise Research Management Environment).

The Oncore database resides on dedicated secure and PHI compliant hardware located in the University of Minnesota (UMN) datacenter (WBOB) All the data servers are managed by the Academic Health Center – Information Systems (AHC-IS) virtual servers which utilize clustered infrastructure to provide real-time failover of virtual servers. All relevant AHC IS procedures related for PHI compliant servers (as required by the Center of Excellence for HIPAA Data) apply to Oncore databases.

The integrated data will be stored in PHI compliant servers managed by AHC IS with access given to those authorized users in the Clinical and Translation Science Institute Informatics team (CTSI BPIC and MCC CISS). The informatics team will grant the IRB approved study team members access to data.

Additional data about correlative laboratory samples generated by the Masonic Cancer Center Translational Therapy Laboratory (TTL) from the protocol-directed correlative research samples is stored in their Laboratory Information Management System (LIMS).The LIMS database application is also stored on a production server located in the UMN datacenter (WBOB) and is managed by the Academic Health Center

Key study personnel are trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore.

11.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRF) developed within OnCore based on its library of standardized forms. The e-CRF will be approved by study's Principal Investigator and the Biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into OnCore at time of study entry, completing e-CRF based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

11.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at http://z.umn.edu/dmsp

For the purposes of data and safety monitoring, this study is classified as moderate-risk (Phase II). Therefore the following requirements will be fulfilled:

- Twice yearly review by the Masonic Cancer Center Data and Safety Monitoring Council (DSMC) with the understanding the Cancer Protocol Review Committee (CPRC) may require more frequent reporting.
- The PI will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The PI will oversee the submission of all reportable adverse events per the definition of reportable in Section 10.6 to the Masonic Cancer Center's SAE Coordinator, the University of Minnesota IRB and Pfizer.

11.4 Investigational New Drug (IND) Assessment

A commercial formulation of Exemestane will be provided by Pfizer for the purposes of this study. In addition was determined that this study meets all conditions of the exemption criteria found in 21 CFR 312.2. No IND application is required for this study.

11.5 Monitoring

The investigator will permit study-related monitoring, audits, and inspections by IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

11.6 Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at 6 years after the study file is closed with the IRB.

In addition, the Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient.

Please contact the CTO before destroying any study related records.

12 Study Endpoints

12.1 Primary Endpoint

Initial disease response will be assessed 6 weeks after the start of exemestane using the Response Criteria in Solid Tumors (RECIST). Refer to Appendix II.

12.2 Secondary Endpoints

Toxicity will be assessed from the 1st dose of exemestane through 30 days after the last dose, or the start of a new anti-cancer treatment, whichever is earlier. Toxicity severity will be graded using the Common Toxicity Criteria for Adverse Events (CTCAE) version 4. Attribution and expectedness will be assigned per the definitions found in Section 10.1.

Response duration, progression-free survival and survival will be assessed until 1 year after study enrollment based on the definitions found in RECIST 1.1 (Appendix II).

Quality of life will be assessed by use of PROMIS-29 at baseline, every 3 weeks while on study drug and at the end of treatment visit.

13 Statistical Considerations

13.1 Study Design, Objectives and Endpoints

The goal of this phase II study is to estimate the probability of response after treatment of exemestane in post-menopausal women with advanced non-small cell lung cancer progressing while on immune checkpoint blockade. The primary endpoint of treatment response will be assessed at 6 weeks after the start of treatment using RECIST criteria. Secondary endpoints include the proportion of toxicities through 30 days after the last dose or start of new treatment as described in Section 10.2.2, disease-control as measured by response duration, progression-free and overall survival through 12 months from study enrollment and quality of life scores as measured by PROMIS-29 at baseline, every 3 weeks during treatment and at the end of treatment visit. The primary endpoint of response will be evaluated using a two-stage design.

Stage 1 will enroll 10 patients. If 2 or more patients have an objective response after completion of stage 1, an additional 19 patients will be enrolled in stage 2 for a total of 29 patients. If the total number of patients responding is 4 or greater, the treatment will be considered worthy of further investigation.

13.2 Sample Size

Sample size is based on testing our primary endpoint using Simon's optimal two stage design with a type I error of 5% and power of 80%.[30] Our null hypothesis is that the response is ≤5% (as all will be progressing on anti-PD1 therapy) and our alternative hypothesis is that response is ≥20%. If the treatment is truly not effective, there is a 5% chance of concluding that the drug is effective while if the treatment is truly effective, there is a 20% chance of concluding that it is not effective. Up to 10 patients will be enrolled per year.

13.3 Statistical Analysis

The primary endpoint of response will be estimated with a simple proportion and a 95% confidence interval. The secondary endpoints of survival and progression-free survival will be estimated with Kaplan-Meier curves. Disease control will be assessed with descriptive statistics and plots such as medians, ranges, interquartile ranges and box-plots. Toxicities will be assessed with descriptive statistics and plots such as simple proportions and bar graphs. Quality of life scores, as measured by PROMIS, will be evaluated descriptively at baseline, every 3 weeks during and at the final visit using medians, ranges, interquartile ranges and boxplots to look for trends in various areas measured by PROMIS. Analysis of correlative objectives will involve assessment of associations of baseline measurements of five biomarkers from tumor tissue and clinical outcome. Biomarkers will be evaluated by evaluation of quartiles with subsequent dichotomization and then comparison by response using a Chi-square test or Fisher's exact test depending on sample size. Evaluation of biomarkers is primarily descriptive and will be used in the planning of future studies both for selection criteria and validation. Six biomarkers from blood will similarly be assessed; however, these measurements will be assessed at individual post-treatment time-points as well. If warranted, repeated measures analyses may be used to look at measurements over time. There is currently no plan to demonstrate that the biomarkers could be used as surrogate endpoints but rather if associations exist for future evaluation.

13.4 Monitoring Guidelines

Monitoring guidelines are developed to monitor excess toxicity using a continuous monitoring strategy based on an adaptation of Pocock stopping boundaries.[31] In the event that a stopping rule is triggered, enrollment will be halted in the affected Treatment Plan. The Treatment Plan will be reviewed by the study committee (PI, co-I's and Statistician) and a decision made about the future of the study. The IRB would be notified in the appropriate manner (expedited or at time of annual continuing review).

13.4.1 Grade 4/5 treatment Related Toxicity

The goal is to construct a boundary based on toxicity such that the probability of early stopping is at most 10% if the toxicity rate is equal to 5% with a sample size of 29. Given these parameters, the upper stopping boundary for toxicity is 2 events out of 7 patients, 3 out of 16, 4 out of 28, or 5 at any time. If the true toxicity rate is as high as 20% then chance of early stopping is 87% and the expected sample size is 13.5.

13.4.2 Grade 3/4/5 Pneumonitis, Colitis, Nephritis, Myocarditis or Hepatitis

The goal is to construct a boundary based on toxicity such that the probability of early stopping is at most 10% if the toxicity rate is equal to 4% with a sample size of 29. Given these parameters, the upper stopping boundary for toxicity is 2 events out of 8 patients, 3 out of 19 or 4 at any time. If the true toxicity rate is as high as 20% then chance of early stopping is 90% and the expected sample size is 11.5.

Due to the addition of stopping rules, it is understood that the overall power may be slightly reduced for this study.

14 Conduct of the Study

14.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

14.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

14.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the consent

document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

15 References

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Appendix I – ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

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Appendix II - Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)

Definitions:

Evaluable for Response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters:

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest

lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up

corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Appendix III– Strong CYP3A4 Inducers

Most common strong CYP3A4 Inducers

Carbamezepine
Dexamethasone
Ethosuximide
Glucocorticoids
Griseofulvin
Phenytoin
Primidone
Progesterone
Rifabutin
Rifampin
Nafcillin
Nelfinavir
Nevirapine
Oxcarbazepine
Phenobarbital
Phenylbutazone
Rofecoxib (mild)
St John's wort
Sulfadimidine
Sulfinpyrazone
Troglitazone

Appendix IV – Potential Risks of Standard of Care Anti-PD1/PDL-1 Therapy

Source: Micromedex

Pembrolizumab

Common

- **Dermatologic:** Pruritus (11% to 28%), Rash, Immune-mediated (17% to 42%)
- **Endocrine metabolic:** Hypercholesterolemia (Non-small cell lung cancer, 20%), Hyperglycemia (40% to 48%), Hypertriglyceridemia (23% to 25%), Hypoalbuminemia (32% to 34%), Hyponatremia (10% to 38%)
- **Gastrointestinal:** Constipation (15% to 51%), Decrease in appetite (16% to 31%), Diarrhea (14% to 37%), Nausea (13% to 68%)
- **Hepatic:** Alkaline phosphatase raised (Non-small cell lung cancer, 26%), AST/SGOT level raised (20% to 24%)
- **Musculoskeletal:** Arthralgia (10% to 18%), Musculoskeletal pain (21% to 32%)
- **Respiratory:** Cough (15% to 24%), Dyspnea (11% to 39%)
- **Other:** Fatigue (20% to 71%)

Serious

- **Cardiovascular:** Vasculitis, Immune-mediated (Less than 1%)
- **Dermatologic:** Bullous pemphigoid (Less than 1%), Erythroderma (Less than 1%)
- **Endocrine metabolic:** Hypophysitis, Immune-mediated (0.6%)
- **Hematologic:** Anemia, Grade 3 or 4 (2% to 8%), Hemolytic anemia, Immune-mediated (Less than 1%)
- **Hepatic:** Hepatitis, Immune-mediated (0.7%), Pancreatitis, Immune-mediated (Less than 1%), Veno-occlusive disease of the liver, Immune-mediated (9%)
- **Immunologic:** Graft versus host disease, Immune-mediated (26%)
- **Musculoskeletal:** Eaton-Lambert syndrome, Rhabdomyolysis
- **Neurologic:** Confusional state (Head and neck cancer, 2% or more)
- **Ophthalmic:** Optic neuritis, Uveitis, Immune-mediated (Less than 1%)
- **Renal:** Nephritis, Immune-mediated (0.3%), Renal failure
- **Respiratory:** Pleural effusion (2% or more), Pneumonia (2% or more), Pneumonitis, Immune-mediated (3.4%), Respiratory failure (Head and neck cancer, 2% or more)
- **Other:** Infusion reaction (0.2%), Sepsis (Up to 10%)

Nivolumab

Common

- **Dermatologic:** Pruritus (10% to 28%), Rash
- **Endocrine metabolic:** Hyperglycemia (Urothelial carcinoma, 42%), Hyperkalemia (15% to 30%), Hypocalcemia (23% to 29%), Hyponatremia (25% to 41%), Serum cholesterol raised (Renal cell carcinoma, 21%), Serum triglycerides raised (Renal cell carcinoma, 32%)
- **Gastrointestinal:** Abdominal pain, Constipation (10% to 23%), Decrease in appetite (22% to 28%), Nausea (20% to 28%), Vomiting (12% to 28%)
- **Hematologic:** Anemia, All Grades (39% to 40%), Lymphocytopenia, All Grades (37% to 42%)
- **Hepatic:** Alkaline phosphatase raised (Urothelial carcinoma, 33%), ALT/SGPT level raised (Urothelial carcinoma, 18%), AST/SGOT level raised (Urothelial carcinoma, 24%)
- **Musculoskeletal:** Arthralgia (10% to 21%), Backache (Renal cell carcinoma, 21%), Musculoskeletal pain
- **Neurologic:** Asthenia, Headache (17% to 23%), Peripheral neuropathy (Up to 12%)
- **Renal:** Serum creatinine raised (Urothelial carcinoma, 39%)
- **Respiratory:** Cough (10% to 36%), Dyspnea (2% to 20%), Upper respiratory infection
- **Other:** Fatigue (49%)

Serious

- **Cardiovascular:** Myocarditis, Immune-mediated (Less than 1%), Vasculitis, Immune-mediated (Less than 1%)
- **Dermatologic:** Rash, Immune-mediated (9% to 22.6%), Stevens-Johnson syndrome, Immune-mediated, Toxic epidermal necrolysis, Immune-mediated
- **Endocrine metabolic:** Adrenal insufficiency, Immune-mediated (1% to 5%), Diabetic ketoacidosis, Hypercalcemia (Renal cell carcinoma, 19%), Hyperthyroidism, Immune-mediated (2.7% to 8%), Hypophysitis, Immune-mediated (0.6% to 9%), Hypopituitarism, Immune-mediated (Less than 1%), Hypothyroidism, Immune-mediated, Thyroiditis, Immune-mediated, Type 1 diabetes mellitus, Immune-mediated (0.9% to 1.5%)
- **Gastrointestinal:** Colitis, Immune-mediated (Monotherapy, 2.9%; combined with ipilimumab, 26%), Diarrhea (17% to 52%), Duodenitis, Immune-mediated (Less than 1%), Gastritis, Immune-mediated (Less than 1%), Pancreatitis, Immune-mediated (Less than 1%), Perforation of colon (Less than 10%)
- **Hematologic:** Anemia, Grade 3 or 4 (1.1% to 8%), Lymphocytopenia, Grade 3 or 4 (4.3% to 9%), Neutropenia, Grade 3 or 4 (1.1%)
- **Hepatic:** Hepatitis, Immune-mediated (1.8% to 13%)
- **Immunologic:** Histiocytic necrotizing lymphadenitis, Immune-mediated (Less than 1%), Sarcoidosis, Immune-mediated (Less than 1%)
- **Musculoskeletal:** Eaton-Lambert syndrome, Immune-mediated (Less than 1%), Myositis, Immune-mediated (Less than 1%), Rhabdomyolysis, Immune-mediated (Less than 1%)
- **Neurologic:** Demyelination of spinal cord, Immune-mediated (Less than 1%), Encephalitis, Immune-mediated (0.2%), Guillain-Barré syndrome, Immune-mediated (Less than 1%), Neuropathy, Immune-mediated (Less than 1%)
- **Ophthalmic:** Uveitis, Immune-mediated (Less than 1%)
- **Renal:** Nephritis, Immune-mediated, Renal impairment, Immune-mediated, Urinary tract infectious disease (Urothelial carcinoma, 17%)
- **Respiratory:** Pleural effusion (2% or greater), Pneumonitis, Immune-mediated (3.1% to 6%), Pulmonary embolism (Non-small cell lung cancer, 4.2%), Respiratory failure (2% or greater), Respiratory tract infection (2% or greater)
- **Other:** Sepsis (2% or greater)

Atezolizumab

Common

- **Gastrointestinal:** Constipation (15% to 21%), Decrease in appetite (24% to 35%), Diarrhea, Immune-mediated (18% to 24%), Nausea (22% to 25%)
- **Respiratory:** Cough (14% to 30%), Dyspnea (12% to 32%)
- **Other:** Fatigue (52%)

Serious

- **Cardiovascular:** Myocarditis (Up to 1%)
- **Endocrine metabolic:** Adrenal insufficiency, Immune-mediated (0.4%), Diabetes mellitus, Immune-mediated (0.2% to 0.3%), Hyperthyroidism (0.6% to 1.1%), Hypophysitis, Immune-mediated (0.2%), Hypothyroidism (2.5% to 4.2%)
- **Gastrointestinal:** Abdominal pain (15% to 17%), Colitis, Immune-mediated, Pancreatitis, Immune-mediated (0.1%)
- **Hepatic:** Hepatitis, Immune-mediated (0.9% to 1.3%)
- **Musculoskeletal:** Eaton-Lambert syndrome, Myasthenia gravis, Immune-mediated
- **Neurologic:** Encephalitis, Guillain-Barré syndrome, Immune-mediated, Meningitis
- **Renal:** Hematuria (14%), Urinary tract infectious disease (17% to 22%)
- **Respiratory:** Interstitial lung disease, Pneumonitis, Immune-mediated
- **Other:** Fever (14% to 21%), Infectious disease (37.7% to 43%), Infusion reaction (1.6% to 1.7%)

Appendix V - Daily Drug Log

Patient ID: _____

The study drug exemestane should be taken with a meal once a day, every day until you are told to stop. If you forget to take a dose by more than 8 hour after the scheduled time or vomit after you take a dose, you should skip the dose and only take the next schedule dose. If this occurs, record a "0" in the time taken column and indicate the reason the dose was missed under the notes column.

Please bring this completed drug log and your study drug bottles (including any unused medication) with you to each appointment. If you have any questions, please contact the study coordinator _____ at _____.

date	**time of dose**	**verify 1 tablet taken (if dose missed record 0)**	**side effects and notes**

date	**time of dose**	**verify 1 tablet taken (if dose missed record 0)**	**side effects and notes**

Upon return of the completed log and drug reconciliation:

Research Staff Signature: _____ Date Reviewed: _____

Appendix VI - PROMIS -29 Profile

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Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
1	Are you able to do chores such as vacuuming or yard work?	☐	☐	☐	☐	☐
2	Are you able to go up and down stairs at a normal pace?	☐	☐	☐	☐	☐
3	Are you able to go for a walk of at least 15 minutes?	☐	☐	☐	☐	☐
4	Are you able to run errands and shop?	☐	☐	☐	☐	☐
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
5	I felt fearful	☐	☐	☐	☐	☐
6	I found it hard to focus on anything other than my anxiety	☐	☐	☐	☐	☐
7	My worries overwhelmed me	☐	☐	☐	☐	☐
8	I felt uneasy	☐	☐	☐	☐	☐
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
9	I felt worthless	☐	☐	☐	☐	☐
10	I felt helpless	☐	☐	☐	☐	☐
11	I felt depressed	☐	☐	☐	☐	☐
12	I felt hopeless	☐	☐	☐	☐	☐
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
13	I feel fatigued	☐	☐	☐	☐	☐
14	I have trouble starting things because I am tired	☐	☐	☐	☐	☐

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	Fatigue **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
15	How run-down did you feel on average? ...	☐	☐	☐	☐	☐
16	How fatigued were you on average?	☐	☐	☐	☐	☐
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
17	My sleep quality was	☐	☐	☐	☐	☐
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
18	My sleep was refreshing.	☐	☐	☐	☐	☐
19	I had a problem with my sleep	☐	☐	☐	☐	☐
20	I had difficulty falling asleep	☐	☐	☐	☐	☐
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
21	I have trouble doing all of my regular leisure activities with others	☐	☐	☐	☐	☐
22	I have trouble doing all of the family activities that I want to do	☐	☐	☐	☐	☐
23	I have trouble doing all of my usual work (include work at home)	☐	☐	☐	☐	☐
24	I have trouble doing all of the activities with friends that I want to do	☐	☐	☐	☐	☐
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
25	How much did pain interfere with your day to day activities?	☐	☐	☐	☐	☐
26	How much did pain interfere with work around the home?	☐	☐	☐	☐	☐
27	How much did pain interfere with your ability to participate in social activities?.	☐	☐	☐	☐	☐
28	How much did pain interfere with your household chores?	☐	☐	☐	☐	☐

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Pain Intensity

In the past 7 days…

29	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst imaginable pain**

