CDK4 and CDK6 Inhibitor

Aberniclib, LY2835219

Drug Discovery Platform: Cancer Cell Signaling
The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

### JUNIPER: A Randomized Phase 3 Study of Abemaciclib Plus Best Supportive Care Versus Erlotinib Plus Best Supportive Care in Patients With Stage IV NSCLC With a Detectable KRAS Mutation Who Have Progressed After Platinum-Based Chemotherapy*

#### Key Inclusion Criteria
- Stage IV non-small cell lung cancer (NSCLC)
- Detectable mutations in codons 12 or 13 of the KRAS oncogene by an investigational assay at the central study laboratory. A KRAS positive mutation result in codons 12 or 13 of the KRAS oncogene from tumor tissue per local laboratory will be permitted in no more than 10% of the randomized patients
- Must have progressed after platinum-based chemotherapy (with or without maintenance therapy) and have received one additional therapy that may include an immune checkpoint inhibitor or other anti-cancer therapy for advanced and/or metastatic disease, or is judged by the physician as ineligible for further standard-second line chemotherapy
- Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Discontinuation of all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and investigational therapy) for at least 21 or 14 days for myelosuppressive or nonmyelosuppressive agents, respectively, prior to receiving study drug

#### Key Exclusion Criteria
- Prior treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days of the initial dose of study drug for a nonmyelosuppressive or myelosuppressive agent, respectively
- History of any of the following conditions: Presyncope or syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest
- Presence of unstable central nervous system (CNS) metastasis. Histories of CNS metastasis or stable CNS metastases are allowed (no longer requiring active therapy such as stered medications). Participants with a history of CNS metastases must have a brain scan (eg, magnetic resonance imaging) within 28 days of randomization to document stability, even if there have been no changes in symptoms.

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02152631].

*This clinical trial is being conducted globally.

#### Primary endpoints:
- Progression-free survival
- Overall survival

#### Randomization 3:2

<table>
<thead>
<tr>
<th>KRAS mutant stage IV NSCLC previously progressed on platinum-based therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg abemaciclib PO Q12H + best supportive care†</td>
</tr>
<tr>
<td>150 mg erlotinib PO Q24H + best supportive care*</td>
</tr>
</tbody>
</table>

† Participants continue study treatment until development of progressive disease.

CDK4 and CDK6 Inhibitor Abemaciclib, LY2835219
A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Compare NSAI (Anastrozole or Letrozole) Plus Abemaciclib, a CDK4 and CDK6 Inhibitor, or Plus Placebo, and to Compare Fulvestrant Plus Abemaciclib or Plus Placebo in Postmenopausal Women With Hormone-Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer*

Key Inclusion Criteria
- Hormone-receptor-positive (HR+), HER2-negative breast cancer
- Locoregionally recurrent disease not amenable to resection or radiation therapy with curative intent or metastatic disease
- Cohort A must exhibit one of the following:
  - Relapsed with de novo metastatic breast cancer (mBC) and has not received any prior endocrine therapy
  - Cohort B must exhibit one of the following:
    - Relapsed with disease progression while receiving neoadjuvant or adjuvant endocrine therapy, or within 1 year of completion of adjuvant endocrine therapy, with no subsequent endocrine therapy
    - Relapsed with disease progression more than 1 year from completion of adjuvant endocrine therapy and has received no prior endocrine therapy
- Postmenopausal status
- Measurable disease or nonmeasurable bone-only disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function
- Discontinuation of localized radiotherapy for palliative purposes or for lytic lesions at risk of fracture at least 2 weeks prior to randomization and recovered from the acute effects of therapy (until the toxicity resolves to either baseline or at least grade 1) except for residual alopecia or peripheral neuropathy

Key Exclusion Criteria
- Visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis
- Inflammatory breast cancer
- Evidence or history of central nervous system metastasis
- Currently receiving or has previously received chemotherapy for locoregionally recurrent or metastatic breast cancer
- Prior treatment with everolimus or fulvestrant (for cohort B only)
- Prior treatment with a CDK4 and CDK6 inhibitor
- Prior treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days of randomization for a nonmyelosuppressive or myelosuppressive agent, respectively
- Serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study (eg, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn’s disease or ulcerative colitis)
- History of any of the following conditions within the last 12 months:
  - Syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest
  - History of any other cancer (except nonmelanoma skin cancer or carcinoma in situ of the cervix) unless in complete remission with no therapy for a minimum of 3 years
- Active bacterial, fungal, and/or known viral infection

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02763566].

* This clinical trial is being conducted outside the United States.

CDK4 and CDK6 Inhibitor Abemaciclib, LY2835219

Primary endpoint: Progression-free survival

Participants continue study treatment until disease progression.
† Abemaciclib or placebo equivalent is administered PO Q12H on days 1-28 of a 28-day cycle.
‡ Anastrozole or letrozole is administered PO Q24H on days 1-28 of a 28-day cycle.
§ Fulvestrant is administered intramuscularly on day 1 of each cycle and then on day 1 of cycle 2 and beyond.

Women with HR+, HER2-negative locoregionally recurrent or metastatic breast cancer

Cohort A
- Abemaciclib† + NSAI‡
- Placebo† + NSAI‡

Cohort B
- Abemaciclib† + fulvestrant§
- Placebo† + fulvestrant§

Abemaciclib†
Abemaciclib† + fulvestrant§
Placebo† + fulvestrant§
Placebo† + NSAI‡
Abemaciclib† + NSAI‡
Women with HR+, HER2-negative locoregionally recurrent or metastatic breast cancer

Key Inclusion Criteria
- Hormone-receptor-positive (HR+), HER2-negative breast cancer
- Locoregionally recurrent disease not amenable to resection or radiation therapy with curative intent or metastatic disease
- Cohort A must exhibit one of the following:
  - Relapsed with de novo metastatic breast cancer (mBC) and has not received any prior endocrine therapy
  - Cohort B must exhibit one of the following:
    - Relapsed with disease progression while receiving neoadjuvant or adjuvant endocrine therapy, or within 1 year of completion of adjuvant endocrine therapy, with no subsequent endocrine therapy
    - Relapsed with disease progression more than 1 year from completion of adjuvant endocrine therapy and has received no prior endocrine therapy
- Postmenopausal status
- Measurable disease or nonmeasurable bone-only disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function
- Discontinuation of localized radiotherapy for palliative purposes or for lytic lesions at risk of fracture at least 2 weeks prior to randomization and recovered from the acute effects of therapy (until the toxicity resolves to either baseline or at least grade 1) except for residual alopecia or peripheral neuropathy

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.
A Phase 2 Study of Abemaciclib in Patients With Brain Metastases Secondary to Hormone-Receptor-Positive Breast Cancer, Non-small Cell Lung Cancer, or Melanoma*

Key Inclusion Criteria

- Brain metastases secondary to hormone-receptor-positive (HR+) breast cancer, non-small cell lung cancer (NSCLC), or melanoma
- HER2-positive (part A) or HER2-negative (part B) breast cancer
- Part C: HR+ breast cancer, NSCLC, or melanoma with brain lesions clinically indicated for surgical resection as well as consent to provide tissue for drug concentration determination after 5 to 14 days of study drug dosing
- Part D: NSCLC of any subtype
- Part E: Melanoma of any subtype
- Part F: HR+ breast cancer, NSCLC, or melanoma with leptomeningeal metastases
- Parts A, B, D, and E: Must have at least one measurable brain lesion ≥10 mm in the longest diameter
- If receiving concomitant corticosteroids, must be on a stable or decreasing dose for at least 7 days prior to the baseline Gd magnetic resonance imaging
- Karnofsky performance status of ≥70
- Life expectancy of ≥12 weeks

Key Exclusion Criteria

- Requires immediate local therapy for brain metastases
- Receiving enzyme-inducing antiepileptic drugs
- Evidence of significant intracranial hemorrhage
- Evidence of leptomeningeal disease (except part F)
- Experienced more than two seizures within 4 weeks prior to study entry

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02308020].

* This clinical trial is being conducted globally.

Primary endpoint: Objective intracranial response rate

Part A**: HR+, HER2-positive breast cancer
Part B**: HR+, HER2-negative breast cancer
Part D**: HR+, NSCLC
Part E**: Melanoma

Part C**: HR+ breast cancer, NSCLC, or melanoma and clinically indicated for surgical resection (after receiving 5-14 days of treatment)
Part F**: HR+ breast cancer, NSCLC, or melanoma and leptomeningeal metastases (with or without parenchymal brain metastases)

Exploratory

CDK4 and CDK6 Inhibitor Abemaciclib, LY2835219

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.
monarchHER: A Phase 2, Randomized, Multicenter, 3-Arm, Open-Label Study to Compare the Efficacy of Abemaciclib Plus Trastuzumab With or Without Fulvestrant to Standard-of-Care Chemotherapy of Physician’s Choice Plus Trastuzumab in Women With Hormone-Receptor-Positive, HER2-Positive Locally Advanced or Metastatic Breast Cancer*

Key Inclusion Criteria
- Unresectable locally advanced recurrent breast cancer or metastatic breast cancer (all termed advanced disease)
- Primary or metastatic tumor must be hormone-receptor-positive (HR+), HER2-positive breast cancer
- Availability of tumor tissue or willing to undergo pre-treatment biopsy
- Measurable and/or non-measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Previously received at least two HR2-directed therapies for advanced disease
- Must have received trastuzumab extensively in any disease setting
- May have received trastuzumab and/or pertuzumab and/or lapatinib in any disease setting
- Must have received a taxane in any disease setting
- May have received endocrine therapy in any disease setting (excluding fulvestrant)
- Postmenopausal status due to either surgical/natural menopause or ovarian suppression with a gonadotropin-releasing hormone agonist (GnRH; initiated ≥ 28 days prior to start of treatment) or radiation-induced ovarian suppression
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function
- Left ventricular ejection fraction of 50% or higher at baseline (determined by echocardiography or multiple-gated acquisition scanning)
- Negative serum pregnancy test within 14 days prior to randomization and agrees to use medically approved precautions to prevent pregnancy during the study and for 12 weeks following the last dose of abemaciclib if postmenopausal status is due to ovarian suppression due to a GnRH agonist or radiation
- Discontinuation of previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and endocrine therapy), except trastuzumab, for at least 21 or 14 days for myelosuppressive or nonmyelosuppressive agents, respectively
- Discontinuation of previous localized radiotherapy for palliative purposes or for lytic lesions at risk of fracture at least 2 weeks prior to randomization

Key Exclusion Criteria
- Visceral crisis
- Known central nervous system metastases that are untreated or symptomatic or require steroids to control symptoms
- Prior treatment with any CDK4 and CDK6 inhibitor
- Major surgery within 14 days prior to randomization
- Prior treatment with a drug that has not received regulatory approval for any indication within 14 to 21 days of randomization for a nonmyelosuppressive or myelosuppressive agent, respectively
- Serious preexisting medical conditions that would preclude participation in this study
- History within the last 6 months of symptomatic congestive heart failure, myocardial infarction, or unstable angina
- History of any of the following conditions within the last 12 months: Syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02675231].

Arm A: Abemaciclib + fulvestrant + trastuzumab
Arm B: Abemaciclib + trastuzumab
Arm C: Trastuzumab + physician’s choice single-agent chemotherapy

Primary endpoint: Progression-free survival

Participants continue study treatment until discontinuation criteria are met. 
† Abemaciclib is administered PO Q12H on days 1–21 of a 21-day cycle. Trastuzumab is administered intravenously (IV) on day 1 of the cycle, then a maintenance dose on day 1 of each subsequent cycle. Fulvestrant is administered intramuscularly on days 1, 15, and 29, and then every 4 weeks thereafter. Abemaciclib and fulvestrant are administered PO Q12H on days 1–21 of a 21-day cycle. Trastuzumab is administered IV on day 1 of the cycle, then a maintenance dose IV infusion on day 1 of each subsequent cycle. 
‡ Abemaciclib is administered PO Q12H on days 1–21 of a 21-day cycle. Trastuzumab is administered IV on day 1 of the cycle, then a maintenance dose IV infusion on day 1 of each subsequent cycle. 
§ Abemaciclib is administered PO Q12H on days 1–21 of a 21-day cycle. Trastuzumab is administered IV on day 1 of the cycle, then a maintenance dose IV infusion on day 1 of each subsequent cycle. Standard-of-care single-agent chemotherapy of physician’s choice is administered according to the product label.

HR+, HER2-positive advanced breast cancer with prior exposure to ≥2 HER2-directed therapies in the advanced setting

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

CDK4 and CDK6 Inhibitor Abemaciclib, LY2835219
The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

Key Inclusion Criteria
- Hormone-receptor-positive (HR+), HER2-negative breast cancer
- Relapsed or progressed following endocrine therapy
- Received prior treatment with at least two chemotherapy regimens, of which one, but no more than two, were in the metastatic setting
- Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Discontinuation of previous therapies for cancer (including aromatase inhibitors, anti-estrogens, chemotherapy, radiation, and immunotherapy) for at least 21 or 14 days for myelosuppressive or nonmyelosuppressive agents, respectively, prior to receiving study drug
- Recovered from the acute effects of therapy (until the toxicity resolves to either baseline or at least grade 1) except for residual alopecia or peripheral neuropathy
- Adequate organ function
- Negative serum pregnancy test within 7 days prior to the first dose of study treatment and agrees to use highly effective precautions to prevent pregnancy during the study and for 12 weeks following the last dose of study treatment
- Able to swallow oral medication

Key Exclusion Criteria
- Clinical evidence or history of central nervous system metastasis
- Prior treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days prior to randomization of study drug for a nonmyelosuppressive or myelosuppressive agent, respectively
- Major surgery within 14 days prior to randomization
- History of syncope of either unexplained or cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest
- Active bacterial or fungal infection requiring intravenous antibiotics at the time of initiating study treatment and/or detectable viral infection
- Prior treatment with a CDK4 and CDK6 inhibitor
- Preexisting chronic condition resulting in persistent diarrhea
- History of any other cancer (except nonmelanoma skin cancer or carcinoma in situ of the cervix or breast), unless in complete remission with no therapy for a minimum of 3 years

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02747004].

* This clinical trial is being conducted globally.

Abemaciclib† + tamoxifen‡
Abemaciclib† + prophylactic loperamide§
Primary endpoint: Progression-free survival

† Abemaciclib is administered PO Q12H on days 1-28 of a 28-day cycle.
‡ Tamoxifen is administered PO QD over a 28-day cycle.
§ During cycle 1, prophylactic loperamide is administered PO QD with the first dose of abemaciclib. During cycle 2 and beyond, loperamide is administered at the investigator’s discretion and/or if clinically indicated.
The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

Key Exclusion Criteria

- History of any of the following conditions: Syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest
- Central nervous system metastasis with development of associated neurological changes 14 days prior to receiving study drug
- History of any other cancer (except nonmelanoma skin cancer or carcinoma in situ of the cervix or breast) unless in complete remission with no therapy for a minimum of 3 years
- Pregnant, breast-feeding, or expecting to conceive or father children within the duration of the trial through 4 months after last dose of trial treatment
- QTc interval >470 ms on electrocardiogram
- History of interstitial lung disease or pneumonitis
- History of or active autoimmune disease or other syndrome that requires systemic steroids or autoimmune agents for the past 2 years
- Prior anti-PD-1, anti-PD-L1, or anti-CTLA4 agent
- Prior therapy with a CDK4 and CDK6 inhibitor
- Active bacterial, fungal, and/or known viral infection

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02779751].

* This clinical trial is being conducted globally in partnership with Merck Sharp & Dohme Corp.
A Phase 1b Study of Abemaciclib in Combination With Therapies for Patients With Metastatic Breast Cancer*

Key Inclusion Criteria
- Parts A to E and G: Hormone-receptor-positive, HER2-negative metastatic breast cancer (mBC)
- Part F: HER2-positive mBC
- Parts A and B: Must not have received prior systemic endocrine therapy for metastatic disease, except for ongoing therapy with letrozole (part A) or anastrozole (part B)
- Part C: May have received prior systemic endocrine therapy for metastatic disease and may be receiving ongoing therapy with tamoxifen
- Parts D and E: Must have received prior systemic endocrine therapy with at least one nonsteroidal aromatase inhibitor (anastrozole or letrozole) for metastatic disease and may be receiving ongoing therapy with exemestane (part D) or either exemestane or exemestane + everolimus (part E)
- Part F: Must have received at least one chemotherapy regimen for metastatic disease and may be receiving ongoing therapy with trastuzumab
- Part G: May have received prior systemic endocrine therapy with at least one nonsteroidal aromatase inhibitor (anastrozole or letrozole) for metastatic disease
- Female ≥ 18 years of age. For all parts except part F: Must have either postmenopausal status or premenopausal status if continuing or beginning ovarian suppression with a luteinizing hormone-releasing hormone agonist
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Discontinuation of all previous therapies for breast cancer, except for ongoing corresponding combination therapy, for at least 21 or 14 days for myelosuppressive or nonmyelosuppressive agents, respectively, prior to receiving study drug(s) and recovery from the acute effects of therapy
- Parts A to F: Measurable or nonmeasurable disease, but evaluable bone disease, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Part G: Measurable disease as defined by RECIST version 1.1
- Adequate organ function

Key Exclusion Criteria
- mBC with visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis
- Parts A to E and G: Prior systemic chemotherapy for metastatic disease
- Prior therapy with a CDK4 and CDK6 inhibitor and, for part G, fulvestrant or any PI3K/mTOR inhibitor (including LY3023414)
- Intolerant of the standard therapy drug(s) administered in a specific part of the study
- Central nervous system metastasis without prior radiotherapy or either radiotherapy or development of neurological changes ≤ 14 days prior to receiving study treatment
- Part G: - Type 1 diabetes mellitus or a history of gestational diabetes mellitus. Patients with type 2 diabetes mellitus are eligible if adequate control of blood glucose level is obtained with oral therapy as documented by HbA1c < 7% - Baseline electrocardiogram (obtained from day -14 to day -1) with any of the following abnormal findings: Ventricular arrhythmia, evidence of acute myocardial ischemia, heart block (of any degree), or QTc prolongation (defined as Bazett-corrected QT interval ≥ 450 ms)

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02057133].

*This clinical trial is being conducted in the United States.

| Part A: | Abemaciclib® with letrozole |
| Part B: | Abemaciclib® with anastrozole |
| Part C: | Abemaciclib® with tamoxifen |
| Part D: | Abemaciclib® with exemestane |
| Part E: | Dose escalation |
| Cohort 1: | Abemaciclib dose 1 with exemestane +/- everolimus |
| Cohort 2: | Abemaciclib dose 2 with exemestane +/- everolimus |
| Dose confirmation: | Abemaciclib® MTD with exemestane +/- everolimus |
| Part F: | Dose escalation |
| Cohort 1: | Abemaciclib dose 1 with trastuzumab |
| Cohort 2: | Abemaciclib dose 2 with trastuzumab |
| Dose confirmation: | Abemaciclib® MTD with trastuzumab |
| Part G: | Dose escalation |
| Cohort 1: | Abemaciclib dose 1 with LY3023414 + fulvestrant |
| Cohort 2: | Abemaciclib dose 2 with LY3023414 + fulvestrant |
| Dose confirmation: | Abemaciclib® with LY3023414 MTD + fulvestrant |

Primary endpoint: Safety and tolerability of abemaciclib in combination with agents in parts A to G

† Abemaciclib and LY3023414 are administered PO Q12H

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.
Key Inclusion Criteria
- Stage IV non-small cell lung cancer (NSCLC). All participants with nonsquamous NSCLC with epidermal growth factor receptor-activating mutations or anaplastic lymphoma kinase alterations should have received and progressed after appropriate tyrosine kinase inhibitor therapy prior to enrollment.
- Part A: Nonsquamous subtypes only. The participant must have received one to three prior therapies, including one platinum-based chemotherapy for advanced/metastatic NSCLC. Participants who have received pemetrexed as first-line or maintenance therapy must be ≥3 months after treatment for determining eligibility.
- Part B: Any subtype. The participant must have received two to three prior therapies for advanced/metastatic NSCLC.
- Part C: Any subtype. The participant must have received two to three prior therapies for advanced/metastatic NSCLC. If the participant has received prior treatment with any phosphoinositide 3-kinase or mammalian target of rapamycin inhibitor (mTORi), they must be ≥3 months after treatment for determining eligibility.
- Part E: Any subtype. The participant must have received one to three prior therapies for advanced/metastatic NSCLC.
- Measurable or nonmeasurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Discontinuation of all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and investigational therapy) for at least 21 or 14 days for myelosuppressive or nonmyelosuppressive agents, respectively, prior to receiving study drug and recovery from the acute effects of therapy (treatment-related toxicity resolved to baseline) except for residual alopecia.
- Malos and females with reproductive potential must agree to use medically approved contraceptive precautions during the trial and for 3 or 6 months depending on treatment arm following the last dose of study drug. Females with childbearing potential must have a negative serum pregnancy test within 3 to 7 days depending on treatment arm of the first dose of study drug.
- Male patients must have a negative serum pregnancy test within 3 to 7 days depending on treatment arm of the first dose of study drug and be surgically sterilized or use reliable contraception for at least 3 months following the last dose of study drug.
- Discontinuation of all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and investigational therapy) for at least 21 or 14 days for myelosuppressive or nonmyelosuppressive agents, respectively, prior to receiving study drug and recovery from the acute effects of therapy (treatment-related toxicity resolved to baseline) except for residual alopecia.
- Patients with controlled atrial fibrillation for ≥6 months prior to enrollment.
- Part A: Nonsquamous subtypes only. The participant must have received one to three prior therapies, including one platinum-based chemotherapy for advanced/metastatic NSCLC. Participants who have received pemetrexed as first-line or maintenance therapy must be ≥3 months after treatment for determining eligibility.
- Part B: Any subtype. The participant must have received two to three prior therapies for advanced/metastatic NSCLC. If the participant has received prior treatment with any phosphoinositide 3-kinase or mammalian target of rapamycin inhibitor (mTORi), they must be ≥3 months after treatment for determining eligibility.
- Part E: Any subtype. The participant must have received one to three prior therapies for advanced/metastatic NSCLC.
- Measurable or nonmeasurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Discontinuation of all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and investigational therapy) for at least 21 or 14 days for myelosuppressive or nonmyelosuppressive agents, respectively, prior to receiving study drug and recovery from the acute effects of therapy (treatment-related toxicity resolved to baseline) except for residual alopecia.
- Malos and females with reproductive potential must agree to use medically approved contraceptive precautions during the trial and for 3 or 6 months depending on treatment arm following the last dose of study drug. Females with childbearing potential must have a negative serum pregnancy test within 3 to 7 days depending on treatment arm of the first dose of study drug.
- Male patients must have a negative serum pregnancy test within 3 to 7 days depending on treatment arm of the first dose of study drug and be surgically sterilized or use reliable contraception for at least 3 months following the last dose of study drug.
- Patients with controlled atrial fibrillation for ≥6 months prior to enrollment.

Key Exclusion Criteria
- History of syncope of unexplained or cardiovascular etiology, cardiac arrest, or ventricular arrhythmia. Subjects with controlled atrial fibrillation for ≥30 days prior to study treatment are eligible.
- Parts A, B, D, and E: Central nervous system (CNS) metastasis with development of associated neurological changes 16 days prior to receiving study drug. Participants may be receiving a stable dose of corticosteroids. Screening of asymptomatic participants without history of CNS metastasis is not required. Participants with untreated CNS metastases are ineligible.
- History of serious uncontrolled intercurrent medical or psychiatric illness.
- History of acute coronary syndromes (including myocardial infarction and angina), coronary angioplasty, or stenting within 6 months prior to enrollment.
- Prior allergic reaction to pembrolizumab.
- History of severe uncontrolled intercurrent medical or psychiatric illness.
- History of severe uncontrolled intercurrent medical or psychiatric illness.
- Prior allergic reaction to pembrolizumab.
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- Prior allergic reaction to pembrolizumab.
- History of severe uncontrolled intercurrent medical or psychiatric illness.
- Prior allergic reaction to pembrolizumab.

Abemaciclib dose is administered every 12 hours.

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02079636].

* This clinical trial is being conducted globally. Part E is being conducted in partnership with Merck Sharp & Dohme Corp.
The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.
CDK4 and CDK6 Inhibitor Abemaciclib, LY2835219

**Target**
Many human tumors acquire alterations, which can lead to the activation of cyclin-dependent kinases (CDKs)—CDK4 and CDK6. These alterations include mutations that directly activate CDK4 and CDK6, gene amplifications, which increase expression of various protein activators such as cyclin D, as well as genetic losses, which reduce expression of protein inhibitors such as p16. These various mechanisms as well as loss of retinoblastoma (Rb) can lead to an enhanced proliferative potential by decreasing dependency on external growth factors and mitogenic signaling pathways, which are required to stimulate growth under normal conditions.2,3

**Molecule**
Abemaciclib (LY2835219) has been shown in vitro to be a selective ATP-competitive inhibitor of CDK4 and CDK6 kinase activity that prevents the phosphorylation and subsequent inactivation of the Rb tumor suppressor protein, thereby inducing G1 cell cycle arrest and inhibition of cell proliferation.4,5

**Clinical Development**
Abemaciclib is being investigated in clinical trials in patients with breast cancer, non-small cell lung cancer, and pancreatic cancer, including a combination clinical trial in immuno-oncology.

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**Study Schemas Not Available**

- [NCT Number Pending] Gastrointestinal Cancer A Study of Abemaciclib Alone or in Combination With Other Agents in Patients With Previously Treated Pancreatic Ductal Adenocarcinoma
- [NCT02450539] Lung Cancer A Study of Abemaciclib (LY2835219) in Participants With Stage IV Squamous Non-small Cell Lung Cancer

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**The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.**


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