# Anti PD-1 mAb Compared to Docetaxel

A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer

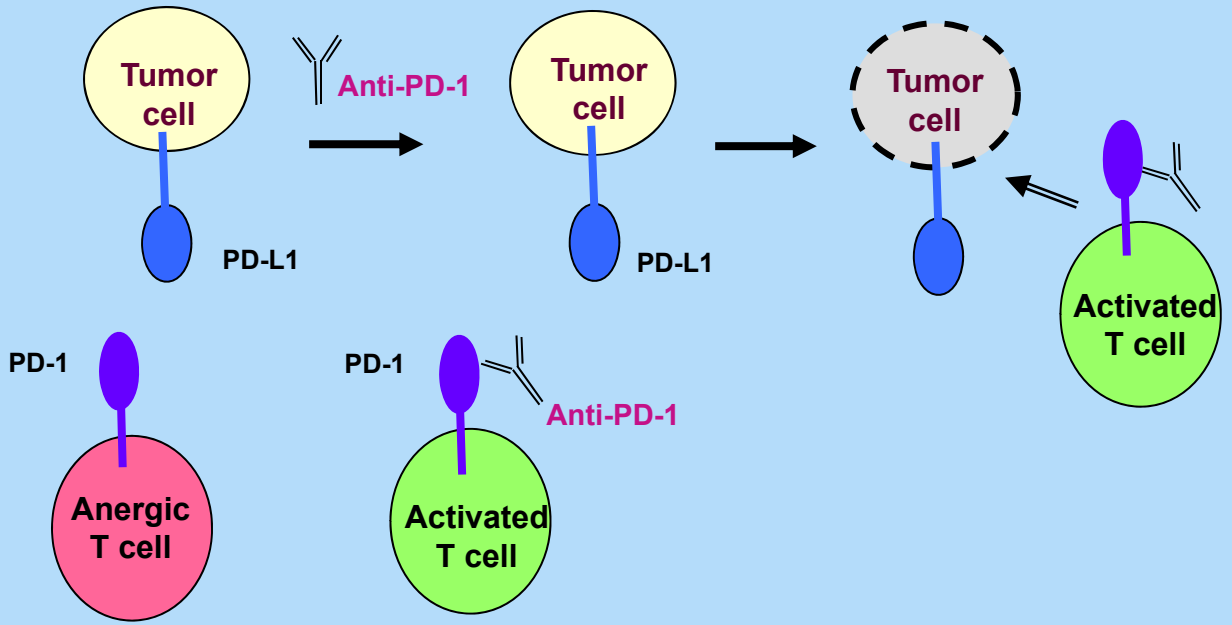
# Immune Tolerance and Cancer

- Immune tolerance is a mechanism of tumor escape from cancer immuno-surveillance
- Causes of immune tolerance
  - Suppressive elements
  - Regulatory Immune cells
  - Suppressive cytokines
  - Inhibitory T cell co-receptors
    - CTLA-4
    - PD-1

# A Study Designed to Determine the Efficacy and Safety of MK-3475 in Targeting the T-cell Checkpoint Pathway

MK-3475 is a highly selective humanized mAb of the IgG4/kappa isotype that is believed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2

1. Anti-PD-1 mAb binds to PD-1
2. Bound anti-PD-1 blocks the interaction between PD-1 and PD-L1 and -L2
3. "Anergic" anti-PD-1 bound cells become activated
4. Activated cells promote immune-mediated tumor cell death




Adapted from Nature Immuno.l Rev. 8:467

# Testing the Hypothesis of Reversing Immune Tolerance to Promote Anti-Tumor Immunity

- Studies which examined 'Inhibiting inhibitors' and reversing immune tolerance by blocking inhibitory T cell co-receptors (CTLA-4 and PD-1)
  - Ipilimumab (IPI) (anti-CTLA-4 mAb)
    - Improved overall survival (OS) in melanoma (MEL) *(Wolkchok NEJM 2011, Hodi NEJM 2010)*
  - Alternative strategy (**anti-PD-1 mAb**)
    - MDX-1106 (BMS PD1 mAb) established proof of concept (POC) of this class of agents in MEL, renal cell carcinoma (RCC), and non-small cell lung cancer (NSCLC) *(Topalian NEJM 2012)*
    - MK-3475 (anti-PD-1 mAb) demonstrated sustained tumor regression in MEL, with mainly grade 1 or 2 toxic effects, both in patients who had received prior treatment with ipilimumab and in those who had not *(Hamid NEJM 2013)*

# Study Objectives

**The study will**

- compare the overall survival (OS) of previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel
- compare progression-free survival (PFS) per RECIST 1.1 by independent radiologists' review of previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel
- Evaluate the safety and tolerability profile of MK-3475 in previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum

# Protocol 001 and Summary of Safety Data

- **Phase I, Protocol 001: Single agent MK-3475 in subjects with progressive locally advanced or metastatic carcinoma, melanoma, and non-small cell lung cancer**

  - Data from 217 patients with previously treated NSCLC who were enrolled and treated according to protocol were used for the analysis of adverse events

  - Efficacy and safety data that were available as of March 3, 2014, were included in all the analyses

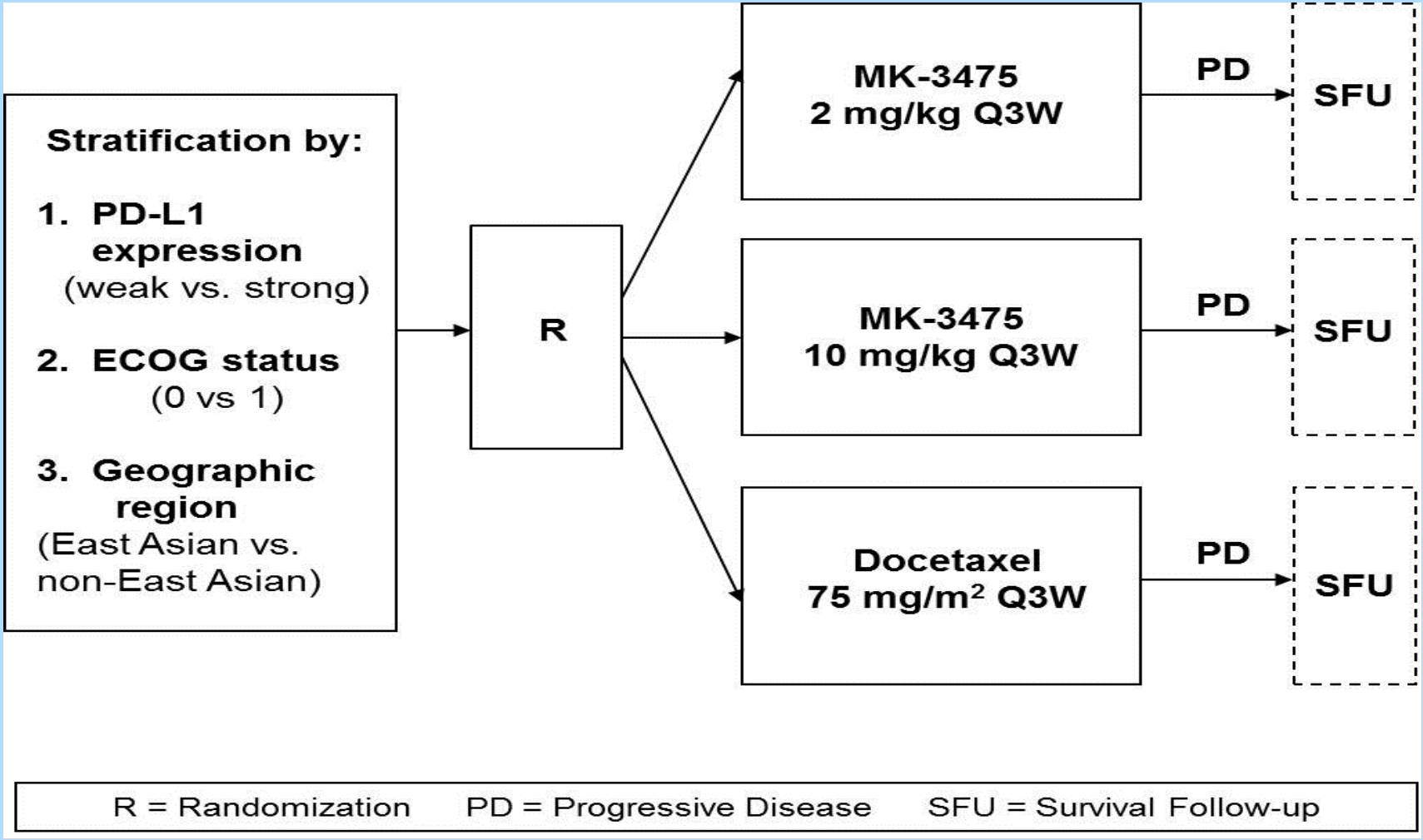
  - Data from Ph1a (dose escalating study) showed no limitation of dose based on tolerability (1, 3, 10 mg/kg with no DLTs)

  - The ongoing safety analysis shows that common adverse events attributed to treatment were fatigue, decreased appetite, pruritis, arthralgia, diarrhea, nausea, pyrexia, rash, hypothyroidism; most of the adverse events were low grade

# Facts About This Trial

- **Study Design**
  - This is a multi-center, worldwide, randomized, adaptively designed Phase II/III trial of intravenous (IV) MK-3475 at two dosing schedules versus docetaxel in patients with NSCLC with PD-L1 positive tumors, who have experienced progression after platinum-containing systemic therapy.
  - Approximately 520-920 patients will be enrolled in a 1:1:1 ratio to receive:
    - MK-3475 at 10 mg/kg Q3 W, or
    - MK-3475 at 2 mg/kg Q3 W, or
    - Docetaxel 75mg/$m^2$ Q3 W

# Study Design




- Treatment cycles are 21 days, with on-study imaging occurring every 9 weeks.

# Facts About This Trial (cont'd)

- Patients may continue on study drug or docetaxel until 2 years of therapy have been administered (or 35 administrations, whichever is later), documented disease progression, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, withdrawal of consent, investigator's decision to withdraw the patient, pregnancy, noncompliance with trial treatment or procedure requirements, or administrative reasons.

- MK 3475 treated patients who attain a complete response (CR) may consider stopping treatment, and can be eligible for re-treatment if they experience disease progression.

- Total study duration is ~ 28 months

# Inclusion Criteria

- Patient is ≥ 18 years of age and has a histologically or cytologically confirmed diagnosis of non-small cell lung cancer (NSCLC) and has at least one measurable lesion as defined by RECIST 1.1

- Patient has experienced investigator determined radiographic progression per RECIST 1.1 of NSCLC after treatment with at least 2 cycles of a platinum-containing doublet for stage IIIB/IV or recurrent disease. Completion of treatment with a platinum-containing doublet as adjuvant therapy within one year of signing informed consent will satisfy the prior treatment requirement.

# Inclusion Criteria (cont'd)

- Patient with an EGFR sensitizing mutation must also be able to demonstrate progression of disease on an EGFR tyrosine kinase inhibitor (TKI), e.g., either erlotinib, gefitinib, or afatinib)

- Patient with an ALK translocation must also be able to demonstrate progression of disease on crizotinib

# Inclusion Criteria (cont'd)

- Patient must be able to provide tissue for PD-L1 biomarker analysis from a newly obtained formalin fixed tumor tissue from a recent biopsy of a tumor lesion not previously irradiated; no systemic antineoplastic therapy may be administered between the PD-L1 biopsy and initiating study medication
  - patients using tyrosine kinase inhibitors prior to treatment on this protocol may continue using these until it is time to begin the appropriate wash out period for these medications

# Exclusion Criteria

- Patient has received prior therapy with docetaxel for NSCLC
- Patient has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)
- Patient has an active autoimmune disease, or a documented history of autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be exception to this rule. Patients that require inhaled steroid or local steroid injections will not be excluded from the study. Patients with hypothyroidism not from autoimmune disease and stable on hormone replacement will not be excluded from the study.
- Patient has participated in another MK-3475 trial

# Safety Profile to Date

- Very common side effects observed in clinical trials with MK-3475 include the following :

  - Diarrhea
  - Fatigue
  - Pruritus
  - Rash
  - Arthralgia
  - Nausea

# Safety Profile to Date (cont'd)

- Other common side effects reported in clinical trials of MK-3475 include:

- Pyrexia
- Abdominal pain/discomfort
- Arthralgia
- Headache
- Flu or flu-like illness
- Dyspnea
- Constipation
- Edema peripheral
- Decreased appetite
- Anemia
- Cough/Productive cough
- Pneumonitis

# Safety Profile to Date (cont'd)

- Other common side effects (cont'd) reported in clinical trials of MK-3475 include:

- Night sweats
- Weight decreased
- Back pain
- Pain in extremity
- Hypothyroidism
- Hyperthyroidism
- Dry eye
- Chills
- Alanine Aminotransferase Increased
- Aspartate Aminotransferase Increased
- Vitiligo
- Vomiting
- Erythema

# Safety Profile to Date (cont'd)

- Serious side effects observed in clinical trials with MK-3475 include the following: *(No event occurred in >1% of everyone treated. Note that some of these events have been previously stated above, so some have occurred more frequently but with less severity.)*
  - Pyrexia
  - Autoimmune nephritis
  - Renal failure
  - Nausea
  - Vomiting
  - Dehydration
  - Confusional State
  - Pneumonitis
  - Pancytopenia
  - Hyperthyroidism
  - Disseminated cryptococcal infection
  - Pericarditis
  - Microscopic colitis
  - Myositis
  - Hypophysitis
  - Pancreatitis
  - Hepatitis

*Do you have a patient who might be a candidate for this clinical trial?*