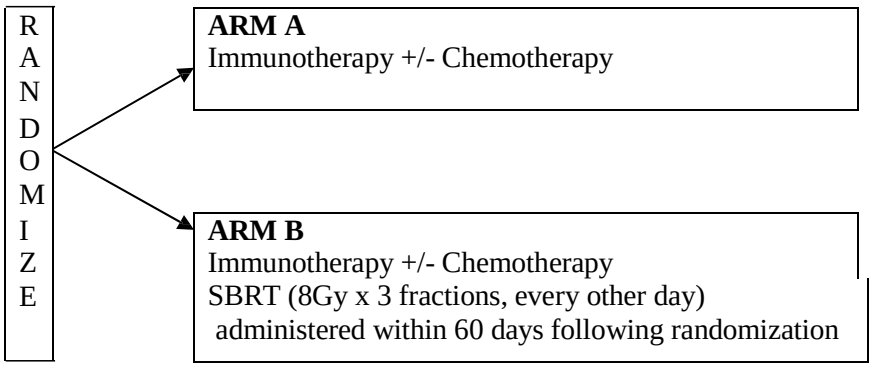
A RANDOMIZED PHASE II/III TRIAL OF MODERN IMMUNOTHERAPY BASED SYSTEMIC THERAPY WITH OR WITHOUT SBRT FOR PD-L1-NEGATIVE, ADVANCED NON-SMALL CELL LUNG CANCER

Eligibility Criteria	**Required Initial Laboratory Values**	
Histologic or cytologic documented NSCLC Stage IV or Stage IIIB-C if not a candidate for chemo-RT	ANC	$\geq 1500/mm^3$
PD-L1 TPS <1%	Platelet count	$\geq 100,000/mm^3$
EGFR, ALK and ROS1 negative (non-squam only)	Calc create Clear	≥ 45 ml/min
Measurable disease	Total Bili	≤ 1.5 x ULN
Age ≥ 18 years	AST/ALT	≤ 2.5 x ULN
ECOG PS 0-2		
No prior treatment per Section 3.2.5		
No comorbid conditions per Section 3.2.6		
Non-pregnant and non-nursing		
No currently active second malignancy		
No hypersensitivity to immunotherapy		
No live vaccine within 30 days		

Schema

1 Cycle = 42 Days



Treatment is to continue for up to 24 months or until disease progression or unacceptable adverse event. Patients will be followed for 5 years or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

3.1 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.2 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers, cervical carcinoma in situ, or DCIS or treated localized (T0-N0, M0) prostate cancer. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for $\geq$ 3 years.
- Patients who would have completed adjuvant chemotherapy within 6 months prior to the start of study treatment

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study and for 5 months for women and 3 months for men after the last protocol treatment due to the teratogenic potential of the therapy utilized in this trial. Include as applicable: Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.3 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ 3.2.1 Documentation of Disease

___ Histologic or cytologic diagnosis of Stage IV NSCLC using version AJCC 8th edition (includes M1a, M1b, and M1c stage disease). Patients with Stage IIIB and IIIC disease are eligible if they are not a candidate for combined chemotherapy

and radiation.

___ **PD-L1 IHC:** PD-L1 expression Tumor Proportion Score (TPS) <1% in tumor cells. If PD-L1 expression TPS is unevaluable or the testing could not be completed patients are not eligible. The assay must have been performed locally by a CLIA (or equivalent) certified laboratory. The type of assay will be recorded.

___ **For non-squamous patients only (adenocarcinoma or adenosquamous): EGFR, ALK and ROS1** testing must be done locally. No patients with known actionable EGFR mutations (except exon 20 insertion), ALK or ROS1 mutations that can be treated with oral tyrosine inhibitors.

___ **3.2.2 Measurable disease** based on RECIST 1.1, including at least two cancerous deposits. At least one deposit must be RECIST measurable (and not to be irradiated) while at least one OTHER deposit (measurable or non-measurable) must meet criteria for SBRT (See Section 7.3)

___ **3.2.3 Age ≥ 18 years**

___ **3.2.4 ECOG Performance Status 0-2**

___ **3.2.5 Prior Treatment**

___ No prior systemic chemotherapy or immunotherapy for advanced NSCLC.

___ No prior treatment with checkpoint inhibitors for metastatic lung cancer.

___ Chemotherapy for non-metastatic disease (e.g., adjuvant therapy) or immunotherapy for locally advanced Stage III disease is allowed if terminated at least 6 months prior to registration.

___ No systemic immunostimulatory or immunosuppressive drugs, including >10mg prednisone equivalent per day, within 2 weeks or 5 half-live of the drug, whichever is shorter.

_ ≥ 1 week since palliative (including CNS) radiotherapy to any tumor site.

___ No prior allogeneic tissue/solid organ transplant.

___ **3.2.6 Comorbid Conditions**

___ No uncontrolled intercurrent illness including, but not limited to, serious ongoing or active infection, symptomatic congestive heart failure, uncontrolled cardiac arrhythmia, unstable angina pectoris, that would limit compliance with study requirements.

___ No current pneumonitis or history of non-infectious pneumonitis that required steroids.

___ HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of registration.

___ No active auto-immune disease that requires systemic therapy within 2 years prior to registration. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid release therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

___ No known history of Hepatitis B (defined as HBsAg reactive) or known Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

___ No patients with symptomatic central nervous system metastases and/or carcinomatous meningitis. Patients with small asymptomatic brain metastases are

eligible as are patients with treated brain metastases that require no steroids.

___ **3.2.7 Not pregnant and not nursing,** because this study involves radiation as well as potentially chemotherapy which have known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative urine or serum pregnancy test done ≤ 7 days prior to registration is required.

___ **3.2.8 No patients with a "currently active" second malignancy that is progressing or has required active treatment within the last 2 years.** Participants with non-melanoma skin cancers or carcinoma in-situ (e.g., breast carcinoma, urothelial carcinoma or cervical cancer in situ) or localized prostate cancer (T1-3, N0, M0) that have undergone potentially curative therapy are eligible.

___ **3.2.9 No hypersensitivity (≥ Grade 3) to immunotherapy and/or any of its excipients.**

___ **3.2.10 No live vaccine within 30 days prior to registration.** Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g.,FluMist®) are live attenuated vaccines and are not allowed. COVID-19 vaccine is allowed.

___ **3.2.11 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC) ≥ 1,500/mm3

Platelet Count ≥ 100,000/mm3

Calc. Creatinine Clearance ≥ 45 mL/min

Total Bilirubin ≤ 1.5 x upper limit of normal (ULN)

AST / ALT ≤ 2.5 x upper limit of normal (ULN)