RANDOMIZED PHASE II STUDY OF NIVOLUMAB WITH OR WITHOUT IPILIMUMAB IN PATIENTS WITH METASTATIC OR UNRESECTABLE SARCOMA

Pre-Registration Eligibility Criteria (see Section 3.2)

Central pathology review submission (see § 3.2.1)

Registration Eligibility Criteria (See Section 3.3)

Histologically confirmed bone or soft tissue sarcoma by central pathology review

Measureable disease as defined in Section 11.0

Locally advanced/unresectable or metastatic disease

≥ 1 prior systemic therapy for sarcoma

No prior therapy with ipilimumab or nivolumab or other agent targeting PD-1, PD-L1 or CTLA-4.

No treatment with biologic therapy, immunotherapy, chemotherapy, investigational agent for malignancy, or radiation ≤ 28 days before study registration. No treatment with nitrosourea or mitomycin ≤ 42 days before study registration. *For GIST, tyrosine kinase inhibitor can be continued for up to 3 days prior to initiation of study treatment.

Required Initial Laboratory Values

Absolute neutrophil count (ANC)	≥ 1500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine	< 1.5 x ULN
Calc. Creatinine Clearance (see Alliance website)	OR ≥ 45 mL/min*
Total Bilirubin	≤ 1.5 x ULN*
AST / ALT	≤ 3 x ULN
TSH	WNL*

*See section 3.3.9

Resolution of any toxic effects of prior therapy (except alopecia) to NCI CTCAE, Version 4.0, grade 1 or less.

No history of the following:

- Active known or suspected autoimmune disease
- Symptomatic, untreated, or uncontrolled brain metastases
- Active autoimmune colitis
- Autoimmune panhypopituitarism
- Autoimmune adrenal insufficiency
- Known active hepatitis B or C (see section 3.3.4 for definition)

No systemic treatment with corticosteroids or other immunosuppressive medications ≤ 14 days of registration.

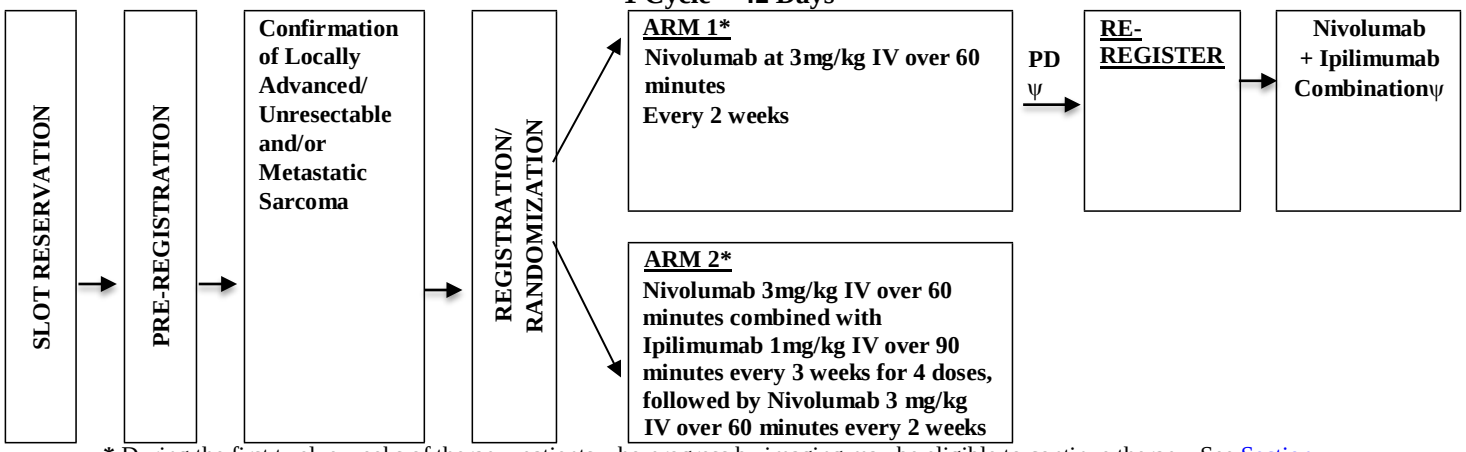
Not pregnant and not nursing (see Section 3.3.6)

Age ≥ 18 years

ECOG performance status 0 or 1

Schema

1 Cycle = 42 Days



***** During the first twelve weeks of therapy, patients who progress by imaging may be eligible to continue therapy. See Section 7.1 for more information.

ψ Nivolumab 3mg/kg IV over 60 minutes combined with Ipilimumab 1mg/kg IV over 90 minutes every 3 weeks for 4 doses total followed by Nivolumab 3 mg/kg IV over 60 minutes every 2 weeks (See Section 3.4, Section 4.7 and Section 7.2 for further instructions).

Treatment is to continue for 104 weeks or until disease progression or unacceptable adverse events. Patients are followed for a maximum of three years post-randomization or until death, whichever comes first.

Please note that vaccinations should be administered prior to therapy (See Section 8.1).

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

3.0 PATIENT SELECTION

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

3.1 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.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol, and the following patients will not be enrolled:

- Medical condition such as uncontrolled infection, 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. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for $\geq$ 3 years.

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).
- Patients with a history of CHf or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs as clinically indicated should be assessed as per the study calendar (see Section 5.0) for appropriateness for participation on this trial.

3.2 Pre-Registration 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 pages.

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 four weeks later would be considered Day 28.

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 Central pathology review submission

Patients must have a FFPE tumor block OR 1 representative H&E and 20 unstained sarcoma tissue slides available for submission for central pathology review. This review is mandatory prior to registration to confirm eligibility. See Section 6.2 for details on slide/block submission.

3.3 Registration Eligibility Criteria

___ 3.3.1 Documentation of Disease

Histologic Documentation:
Prior to Update #06: Patients must have histologically confirmed bone or soft tissue sarcoma by central pathology review.

Effective with Update #06: Patients must have histologically confirmed LPS (only dedifferentiated and pleomorphic. Well differentiated not eligible), UPS/MFH, or GIST.

___ 3.3.2 Disease Status

Measurable disease as defined in Section 11.0.

Locally advanced/unresectable or metastatic disease.

___ 3.3.3 Prior Treatment

- ≥ 1 prior systemic therapy for sarcoma, including adjuvant systemic therapy.
- No prior therapy with ipilimumab or nivolumab, or any agent targeting PD-1, PD-L1 or CTLA-4.
- No treatment with biologic therapy, immunotherapy, chemotherapy, investigational agent for malignancy, or radiation ≤ 28 days before study registration. No treatment with nitrosourea or mitomycin ≤ 42 days before study registration. For GIST, tyrosine kinase inhibitor can be continued for up to 3 days prior to initiation of study treatment.
- Patients should have resolution of any toxic effects of prior therapy (except alopecia) to NCI CTCAE, Version 4.0, grade 1 or less.

___ 3.3.4 No history of the following:

- Active known or suspected autoimmune disease. See Appendix IV for details.
- Patients with HIV are eligible if the lymphocytes > 350 CD4+ cells and no detectable viral load
- Symptomatic, untreated, or uncontrolled brain metastases present.

- Active autoimmune colitis
- Autoimmune panhypopituitarism
- Autoimmune adrenal insufficiency
- Known active hepatitis B or C

Hepatitis B Can be defined as:

1. HBsAg > 6 months
2. Serum HBV DNA 20,000 IU/ml (105copies/ml), lower values 2,000-20,000 IU/ml (104-105 copies/ml) are often seen in HBeAg-negative chronic hepatitis B
3. Persistent or intermittent elevation in ALT/AST levels
4. Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation

Hepatitis C can be defined as:

1. Hepatitis C AB positive
2. Presence of HCV RNA

- Known active pulmonary disease with hypoxia defined as
  1. Oxygen saturation < 85% on room air or
  2. Oxygen saturation <88% despite supplemental oxygen

___ **3.3.5 Concomitant Medications**:

No systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of registration.

3.3.6 Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.

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

___ **3.3.7 Age ≥ 18 years**

___ **3.3.8 ECOG Performance Status 0 or 1.**

___ **3.3.9 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine	≤ 1.5 x upper limit of normal (ULN) **OR**
Calc. Creatinine Clearance	> 45 mL/min*
Total Bilirubin	≤ 1.5 x upper limit of normal (ULN)**
AST / ALT	≤ 3 x upper limit of normal (ULN)
TSH	WNL***

* Using the lean body mass formula only (Modified Cockroft and Gault; Shargel and Yu 1985)

** In absence of Gilbert disease (Total Bilirubin ≤ 3 x ULN with Gilbert). Also, if hyperbilirubinemia is clearly attributed to liver metastases total bilirubin ≤ 3 x ULN is permitted

*** Supplementation is acceptable to achieve a TSH WNL. In patients with abnormal TSH if Free T4 is normal and patient is clinically euthyroid, patient is eligible.

3.4 Re-registration Eligibility Criteria (For patients who crossover from arm 1 nivolumab alone to dual agent nivolumab and ipilimumab upon progression)

___ **3.4.1 Disease Status**

- Measurable disease as defined in Section 11.0.
- Locally advanced/unresectable or metastatic disease.
- Patient MUST have had progressive disease (radiographic or clinical) while on arm 1 single agent nivolumab while registered to A091401.

___ **3.4.2 Prior Treatment**

- Patients removed from any immunotherapy for reasons other than progressive disease, including arm 1 single agent nivolumab of A091401, are NOT eligible for re-registration
- Patients must have completed a minimum of 10 weeks of single agent nivolumab on arm 1 of A091401 to be eligible for re-registration
- Patients must have completed study drug on arm 1 of A091401 (i.e., last dose of nivolumab) ≤ 12 months of re-registration to crossover dual agent therapy
- No treatment with immunotherapy ≤ 21 days before re-registration. No treatment with biologic therapy, chemotherapy, investigational agent for malignancy, or radiation ≤ 28 days before re-registration. No treatment with nitrosourea or mitomycin ≤ 42 days before re-registration.
- Patients should have resolution of any toxic effects of prior therapy (except fatigue and alopecia) to NCI CTCAE, Version 4.0, grade 1 or less, including immune toxicity.

___ **3.4.3 Concomitant Medications**:

No systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of re-registration.

3.4.4 Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.

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

___ **3.4.5 ECOG Performance Status 0 or 1.**

___ **3.4.6 Required Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine	≤ 1.5 x upper limit of normal (ULN) **OR**
Calc. Creatinine Clearance	> 45 mL/min*
Total Bilirubin	≤ 1.5 x upper limit of normal (ULN)**
AST / ALT	≤ 3 x upper limit of normal (ULN)
TSH	WNL***

* Using the lean body mass formula only (Modified Cockroft and Gault; Shargel and Yu 1985)

** In absence of Gilbert disease (Total Bilirubin ≤ 3 x ULN with Gilbert). Also, if hyperbilirubinemia is clearly attributed to liver metastases total bilirubin ≤ 3 x ULN is permitted

*** Supplementation is acceptable to achieve a TSH WNL. In patients with abnormal TSH if Free T4 is normal and patient is clinically euthyroid, patient is eligible.