Appendix

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1: Eligibility Criteria

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).

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.

Registration Eligibility Criteria
Histologic Documentation:
Prior to Update #6: Patients must have histologically confirmed bone or soft tissue sarcoma by central pathology review. Effective with Update #06: Patients must have histologically confirmed LPS, UPS/MFH, or GIST.

Disease Status
Measurable disease as defined in section 11 of protocol. Locally advanced/unresectable or metastatic disease.

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.

No history of the following:

- Active known or suspected autoimmune disease as specified in appendix IV.
- 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:
  - HBsAg > 6 months
  - 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
  - Persistent or intermittent elevation in ALT/AST levels
  - Liver biopsy showing chronic hepatitis with moderate or severe necrosis inflammation
- Hepatitis C can be defined as:
  - Hepatitis C AB positive
  - Presence of HCV RNA

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

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

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.

Age ≥ 18 years
ECOG Performance Status 0 or 1.
Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC)	≥ 1,500/mm3
Platelet Count	≥ 100,000/mm3
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.

2. Protocol Section 11.0: Definitions of Measurable and Non-Measurable Disease

Measurable Disease

- A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.
- A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- A malignant lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions: they have been demonstrated to grow by at least 0.5 cm from measurement prior to radiation.

Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: '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. In addition, lymph nodes that have a short axis < 1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

3. Appendix IV of protocol: Definition of active autoimmune disease

Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, polymyositis, rhabdomyolysis, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease.

Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible.

Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome, vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, psoriasis controlled with topical medication, or conditions not expected to recur in the absence of an external trigger (precipitating event).and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

4. Details in regards to procedures to allow patients to receive combination therapy

Disease Status

- Measurable disease as defined in section 11 (noted above.)
- 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.

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.

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

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.

ECOG Performance Status 0 or 1.

Required Laboratory Values:

Absolute Neutrophil Count (ANC)	≥ 1,500/mm3
Platelet Count	≥ 100,000/mm3
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.

5: Participating sites

Patients were enrolled from 13 participating Alliance networks and two NCTN groups throughout the United States including:1 each of Colorado Cancer Research Program, Sanford NCI Community Oncology, and New Mexico Minority Underserved NCORP; 2 each of North Shore University Health System–Evanston Hospital, NCORP of the Carolinas (Greenville), Heartland Cancer Research (NCORP), and Edwards (West Virginia); Hackensack UMC (3); University of Iowa (4), Southeast Cancer Control Consortium (5); Herbert Irving Comprehensive Cancer Center Columbia University (6); Memorial Sloan Kettering Cancer Center (14), and Washington University (33)]. Patients were also enrolled from other NCTN groups: NRG (2); SWOG (5).

6: Award numbers for funding support

Award Numbers U10CA180821 and U10CA180882 (to the Alliance for Clinical Trials in Oncology), U10CA041287, U10CA045808, U10CA047642, U10CA077440, U10CA007968, U10CA077651, U10CA180791, U10CA180833, U10CA180836, and UG1CA189858.

8: Table 1: Description of Responses During Initial Treatment, by Treatment Arm

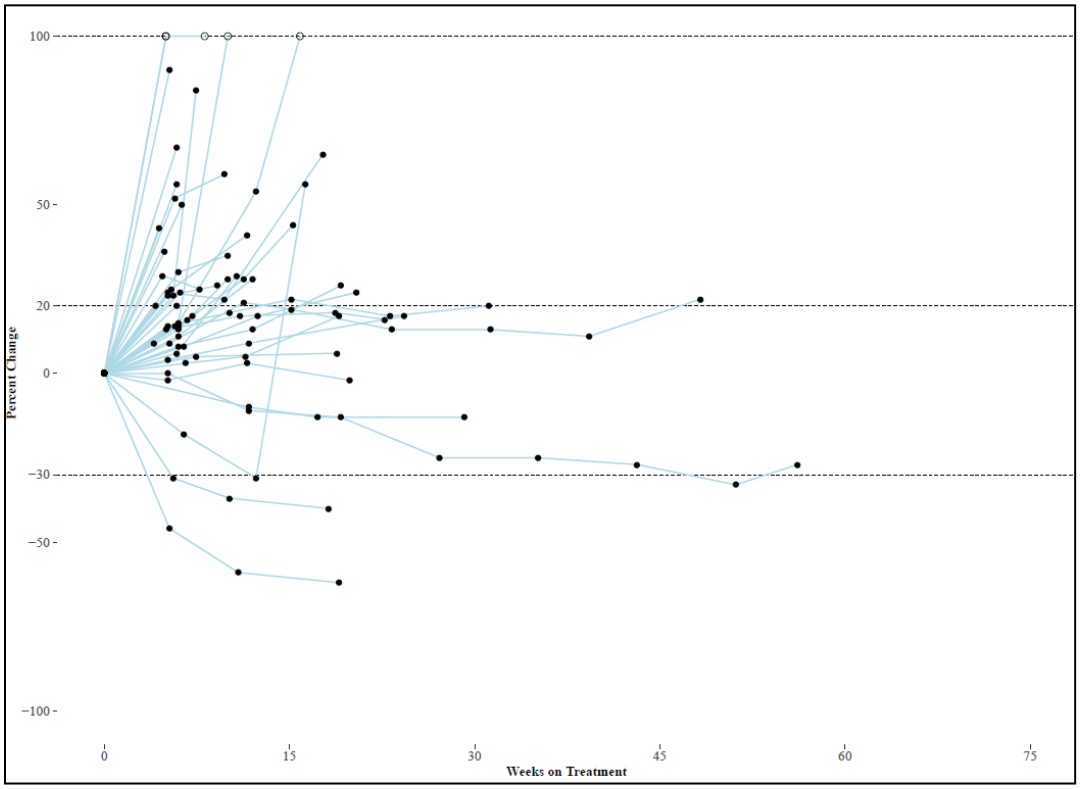
Arm	Patient	Histology	Time to 1st Response[a]	Duration of Response[a]	End of Treatment Reason	Confirmed Response
1[b]	1	**Alevolar**	1.3	2.9	PD	Yes, PR
	2	**Leimoyosarcoma (LMS), non-uterine abdomen/retroperitoneal**	1.2	3.2	PD	Yes, PR
	3	**Other/recurrent sarcoma**	11.8	1.1	PD	No
2[b]	1	**Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma (UPS/MFH)**	1.4	0	Adverse Events	No
	2	**Myxofibrosarcoma**	1.4	14.1	Ongoing	Yes, PR converted to CR within 8.5 months of PR
	3	**UPS/MFH**	1.5	3.2	PD	Yes, PR
	4	**LMS, uterine**	2.6	10.8	Ongoing	Yes, PR converted to CR within 2.5 months
	5	**Angiosarcoma**	1.3	0	AEs	No
	6	**LMS, non-uterine abdomen/retroperitoneal**	4.4	9.2	PD	Yes, PR
	7	**UPS/MFH**	2.8	1.8	Treated for other complicating disease (Radiation)	Yes, PR

a) In months.

b) Arm 1 is monotherapy; Arm 2 is combination therapy.

Figures 1A-B: Spider Plot of Largest Percent Change in the Sum of the Target Lesions/Nodes (RECIST v1·1)

Monotherapy (Figure 1A): Each line in a Spider Plot displays the percent change in the sum of an individual patient's target lesions/nodes (vertical axis), from study entry at each consecutive disease assessment during treatment (horizontal axis). The two horizontal bars represent the criteria for PD (20% increase in tumor size) and response (30% decrease in tumor size for PR; total disappearance of target lesions/nodes for CR). Increases of more than 100% and occurring in 4 patients (two patients overlap in the figure), were truncated to 100% for scaling purposes and noted by using an "o" symbol.



Combination Therapy (Figure 1B): Each line in a Spider Plot displays the percent change in the sum of an individual patient's target lesions/nodes (vertical axis), from study entry at each consecutive disease assessment during treatment (horizontal axis). The two horizontal bars represent the criteria for PD (20% increase in tumor size) and response (30% decrease in tumor size for PR; total disappearance of target lesions/nodes for CR). The 3 patients showing horizontal lines at -100% are those having achieved a CR on multiple consecutive evaluations, one of which is not a true CR per RECIST v1·1 and due to their non-target lesions being classified as non-CR/non-PR.

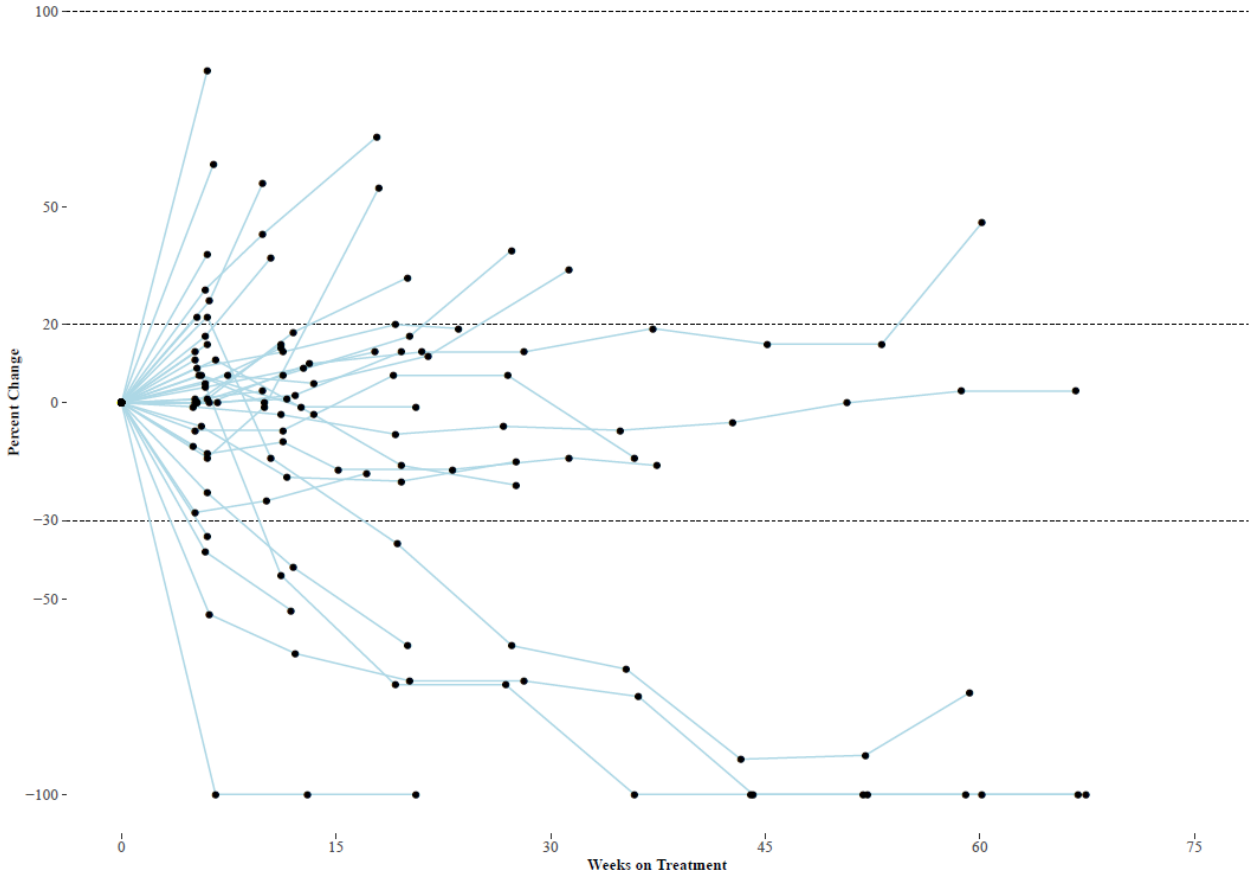


Table 2: Treatment Related AEs, by Arm

	Nivolumab (n=42)[a]				Nivolumab+ Ipilimumab (n=42)			
CTCAE v4.0 AE Term	**Grade 1-2[b]**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2[b]**	**Grade 3**	**Grade 4**	**Grade 5**
Adrenal Insufficiency	-	-	-	-	5 (12%)	1 (2%)	-	-
Alanine Aminotransferase Increased	-	-	-	-	-	1 (2%)	1 (2%)	-
Anemia	5 (12%)	1 (2%)	-	-	5 (12%)	1 (2%)	-	-
Anorexia	5 (12%)	1 (2%)	-	-	4 (10%)	-	-	-
Aspartate Aminotransferase Increased	-	-	-	-	-	-	1 (2%)	-
Dehydration	-	1 (2%)	-	-	-	-	-	-
Diarrhea	-	1 (2%)	-	-	6 (14%)	-	-	-
Dyspnea	-	-	-	-	4 (10%)	-	-	-
Fatigue	12 (29%)	-	-	-	13 (31%)	1 (2%)	-	-
Hyponatremia	-	-	-	-	-	1 (2%)	1 (2%)	-
Hypothyroidism	-	-	-	-	6 (14%)	-	-	-
Lipase Increased	-	2 (5%)	-	-	-	2 (5%)	-	-
Nausea	5 (12%)	-	-	-	5 (12%)	-	-	-
Pain	9 (21%)	-	-	-	6 (14%)	-	-	-
Platelet count decreased	-	1 (2%)	-	-	-	-	-	-
Rash	-	-	-	-	8 (19%)	-	-	-

a) Patients having initiated study treatment.
b) The adverse event is reported if at least 10% of patients experienced a maximum severity of grade 1 or 2 of the specified events.

Table 3: Treatment Related Serious Adverse Events, by Arm

	Nivolumab (n=42)[a]				Nivolumab+ Ipilimumab (n=42)			
CTCAE v4.0 AE Term	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Adrenal Insufficiency	-	-	-	-	2 (5%)	1 (2%)	-	-
Alanine Aminotransferase Increased	-	-	-	-	-	1 (2%)	1 (2%)	-
Anemia	-	1 (2%)	-	-	-	1 (2%)	-	-
Anorexia	-	1 (2%)	-	-	-	-	-	-
Aspartate Aminotransferase Increased	-	-	-	-	-	-	1 (2%)	-
Creatinine Increased	1 (2%)	-	-	-	-	-	-	-
Dehydration	-	1 (2%)	-	-	-	-	-	-
Diarrhea	-	1 (2%)	-	-	-	-	-	-
Fatigue	-	-	-	-	-	1 (2%)	-	-
Fever	1 (2%)	-	-	-	-	-	-	-
Hyponatremia	-	-	-	-	-	1 (2%)	1 (2%)	-
Pain	-	-	-	-	1 (2%)	-	-	-
Platelet count decreased	-	1 (2%)	-	-	-	-	-	-
Pleural Effusion	1 (2%)	-	-	-	-	-	-	-
Pruritus	-	-	-	-	1 (2%)	-	-	-

a) Patients having initiated study treatment.

Table 4: Accruals by site and PI

Network Name	Site Name	Principal Investigator	#
LAPS-MO011 Washington University - Siteman Cancer Center LAPS	MO011 Washington University School of Medicine	Brian Van Tine	**32**
LAPS-NY016 Memorial Sloan-Kettering Cancer Center LAPS	NY016 Memorial Sloan Kettering Cancer Center	William Tap	**14**
COLUMBIA Columbia University Minority Underserved NCORP	NY024 Columbia University/Herbert Irving Cancer Center	Gary Schwartz	**6**
IA018 University of Iowa/Holden Comprehensive Cancer Center	IA018 University of Iowa/Holden Comprehensive Cancer Center	Laith Abushahin	**4**
NJ022 Hackensack University Medical Center	NJ022 Hackensack University Medical Center	Samuel Goldlust	**3**
Southwest oncology group (SWOG)	Kaiser Permanente NCORP, Kaiser Permanente NCAL, San Jose, CA	Sejal Jhatakia, MD	**3**
WV046 Edwards Comprehensive Cancer Center	WV046 Edwards Comprehensive Cancer Center, Huntington, WV	Maria Tria Tirona	**2**
Southwest oncology group (SWOG)	University of Michigan Medical Center, Ann Arbor, MI	Rashmi Chugh, MD	**2**
CCRP Colorado Cancer Research Program NCORP	CO072 Rocky Mountain Cancer Centers-Boulder	Keren Sturtz	**1**
GREENVILLE NCORP of the Carolinas (Greenville Health System NCORP)	SC036 Greenville Health System Cancer Institute-Eastside	Jeffrey Giguere	**1**
GREENVILLE NCORP of the Carolinas (Greenville Health System NCORP)	SC060 Greenville Health System Cancer Institute-Faris	Jeffrey Giguere	**1**
HEARTLAND Heartland Cancer Research NCORP	IL188 Illinois CancerCare-Galesburg	James Wade	**1**
HEARTLAND Heartland Cancer Research NCORP	IL355 Illinois CancerCare-Macomb	James Wade	**1**
IL018 NorthShore University HealthSystem-Evanston Hospital	IL004 NorthShore University HealthSystem-Highland Park Hospital	David Grinblatt	**1**
IL018 NorthShore University HealthSystem-Evanston Hospital	IL018 NorthShore University HealthSystem-Evanston Hospital	David Grinblatt	**1**
LAPS-MO011 Washington University - Siteman Cancer Center LAPS	MO011 Washington University School of Medicine	Nancy Bartlett	**1**
LAPS-OH007 Ohio State University Comprehensive Cancer Center LAPS	OH007 Ohio State University Comprehensive Cancer Center	Clara Bloomfield	**1**
NEWMEXICO New Mexico Minority Underserved NCORP	NM004 University of New Mexico Cancer Center	Olivier Rixe	**1**
SANFORD Sanford NCI Community Oncology Research Program of the North Central Plains	SD004 Sanford Cancer Center Oncology Clinic	Preston Steen	**1**
SCCC Southeast Clinical Oncology Research (SCOR) Consortium NCORP	NC065 Southeastern Medical Oncology Center-Goldsboro	James Atkins	**1**
SCCC Southeast Clinical Oncology Research (SCOR) Consortium NCORP	NC065 Southeastern Medical Oncology Center-Goldsboro	James Atkins	**1**
SCCC Southeast Clinical Oncology Research (SCOR) Consortium NCORP	NC065 Southeastern Medical Oncology Center-Goldsboro	James Atkins	**1**
SCCC Southeast Clinical Oncology Research (SCOR) Consortium NCORP	NC231 Southeastern Medical Oncology Center-Jacksonville	James Atkins	**1**
SCCC Southeast Clinical Oncology Research (SCOR) Consortium NCORP	NC254 Southeastern Medical Oncology Center-Clinton	James Atkins	**1**
NRG	Greenville Health System Cancer Institute	Ki Chung	**1**
NRG	Kaiser Permamente Northwest	Punprapao Boriboonsomsin	**1**