CLINICAL TRIAL REVIEW

Clinical Trial Review is a JDD department designed to provide physicians with information on drugs and devices undergoing clinical testing. It is our goal to inform the reader of the status of select drug and device studies relevant to the practice of dermatology before this information is available through standard channels. To participate in or learn more about these and additional trials, visit www.clinicaltrials.gov.

A Phase 3, Prospective, Open-Label, Multicenter Study of Lymphoseek®-Identified Sentinel Lymph Nodes (SLNs) Relative to the Path Status of Non SLN in an Elective Neck Dissection in Cutaneous Head and Neck and Intraoral Squamous Cell Carcinoma

Sponsored by Navidea Biopharmaceuticals, the purpose of this study is to determine the false negative rate (FNR) associated with Lymphoseek-identified sentinel lymph nodes (SLNs) relative to the pathological status of non-sentinel lymph nodes in elective neck dissection (END) in head & neck SCC. NEO3-06 (this study) is a Phase 3 clinical trial designed to supplement NEO3-05, a Phase 3 clinical trial conducted in patients with breast cancer or melanoma. NEO3-05 is designed to establish Lymphoseek as an effective radio-diagnostic agent to be used in the intraoperative localization of lymph tissue (nodes) in the lymphatic pathway draining the primary site of a tumor.

The primary outcome is to measure a false negative rate in a 72-hour time frame. The secondary outcome is to measure the detection of cancer in the lymph nodes within 30 days.

Exclusions include: Patients that have a diagnosis of squamous cell carcinoma of the head and neck in the following anatomical areas: non-mobile base of the tongue, oral pharynx, nasal pharynx, hypo-pharynx and larynx; patients that are pregnant or lactating; patients that have clinical or radiological evidence of metastatic cancer to the regional lymph nodes; patients with a history of neck dissection, or gross injury to the neck that would preclude reasonable surgical dissection for this study, or radiotherapy to the neck; patients who have had other nuclear imaging studies conducted within 15 days or consenting; patients actively receiving systemic cytotoxic chemotherapy, participating in another investigational drug study or participated within 30 days prior to consenting, or immunosuppressive or anti-monocyte or immunomodulatory therapy.

Inclusion criteria: Patients who have provided written informed consent with HIPAA authorization before participating in the study; have a diagnosis of primary squamous cell carcinoma of the head and neck either cutaneous or intra-oral that is anatomically located in: mucosal lip, buccal mucosa, lower alveolar ridge, upper alveolar ridge, retromolar gingiva (retromolar trigone), floor of the mouth, hard palette or oral (mobile) tongue, stage T1-T4a, N0, M0; clinical nodal staging (N0) has been confirmed by negative results from contrast CT scan or gadolinium-enhanced MRI or lateral and central neck ultrasound. PET scan cannot be used for this evaluation; imaging of the regional nodal basin has been performed within 30 days of the planned lymphadenectomy.

Condition	Intervention
Squamous Cell Carcinoma	**Drug:** 99m-Tc-Tilmanocept (Lymphoseek)
Study ID Numbers: NEO3-06 **ClinicalTrials.gov Identifier:** NCT00911326	

Sentinel Lymph Node Localization and Biopsy for Conjunctival and Eyelid Melanoma

Sponsored by MD Anderson Cancer Center, the goal of this clinical research study is to find the sentinel lymph node (SLN) (s) and biopsy it (them) to see if the patient has small or low volume metastatic disease that would otherwise have been missed. Researchers hope to identify those patients who have microscopic lymph node disease before it becomes clinically obvious. With this technique, researchers could potentially identify occult metastatic disease, which would otherwise go unnoticed until it was too advanced. Patients in this study will have to see the ophthalmologist every three months and have the usual metastatic workup, which is routine for conjunctival/eyelid melanoma.

The primary objectives are to identify the rate of SLN positivity in conjunctival/eyelid melanomas, and determine the false negative rate for SLN biopsy for the same. The secondary objective is to determine the complication rate for this technique, particularly with respect to local ocular and periocular side effects as well as the risk of facial nerve damage.

Exclusion Criteria: Pregnant or nursing females.

Inclusion Criteria: Participants must be 18 years of age or older; histologically documented malignant melanoma of the conjunctiva/eyelid greater than or equal to 1 millimeter in thickness, or those less than 1 mm thick that have evidence of ulceration, mitotic figures or are Clark IV; a CXR, liver enzymes, and a head and neck computed tomography (CT) or magnetic resonance imaging (MRI) negative for evidence of metastasis; must have a negative ultrasound of regional lymph nodes (ie,

within 6 weeks of study enrollment).

Condition	Intervention
Cutaneous Melanoma	**Procedure:** Sentinel Lymph Node Mapping and Biopsy
Study ID Numbers: GSP00-106 **ClinicalTrials.gov Identifier:** NCT00386906	

A Phase 1B/II Study of GDC-0449 (NSC 747691) in Combination With RO4929097, a Gamma-Secretase Inhibitor (GSI) in Advanced/Metastatic Sarcomas

Sponsored by the Nation Cancer Institute, this randomized phase I/II clinical trial is studying the side effects and best dose of gamma-secretase/notch signalling pathway inhibitor RO4929097 when given together with vismodegib and to see how well they work in treating patients with advanced or metastatic sarcoma. Vismodegib may slow the growth of tumor cells. Gamma-secretase/notch signalling pathway inhibitor RO4929097 may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. Giving vismodegib together with gamma-secretase/notch signalling pathway inhibitor RO4929097 may be an effective treatment for sarcoma.

The primary objectives are to determine the maximum-tolerated dose (MTD) of gamma-secretase inhibitor RO4929097 (RO4929097) when given in combination with fixed-dose Hedgehog antagonist GDC-0449 (GDC-0449) which will become the recommended dose for the phase II portion of this study (Phase Ib) II; to assess the progression-free survival (PFS) of the combination of RO4929097 with and without GDC-0449 in two arms of patients with advanced sarcoma (Phase II).

Exclusion criteria: Patients may not receive other investigational agents within 2 weeks of enrollment in this study; patients treated with bevacizumab should be off therapy for 4 weeks; other experimental or immuno therapies should wait for 4 half-lives or 4 weeks, whichever is longer; prior exposure to Notch or Hedgehog inhibitors is not allowed; patients who have not recovered to less than CTCAE grade 2 from prior therapies are ineligible; history of allergic reactions attributed to compounds of similar chemical or biologic composition to GDC-0449 or RO4929097 used in the study; patients taking medications with narrow therapeutic indices that are metabolized by cytochrome P450 (CYP450), including warfarin sodium (Coumadin®) are ineligible; patients on warfarin may be considered for enrollment after cessation of warfarin and appropriate transition to alternate anti-coagulation agents; preclinical studies indicate that RO4929097 is a substrate of cytochrome P450 (CYP)3A4 and inducer of CYP3A4 enzyme activity; caution should be exercised when dosing RO4929097 concurrently with CYP3A4 substrates, inducers, and/or inhibitors; furthermore, patients who are taking concurrent medications that are strong inducers/inhibitors or substrates of CYP3A4 should be switched to alternative medications to minimize any potential risk; the following medications with strong potential for interaction are not allowed: indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone.

Inclusion criteria: Patients must have histologically or cytologically confirmed sarcoma; all Patients must have measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; Eastern Cooperative Oncology Group (ECOG) performance status =< 2 (Karnofsky >= 60%); there is a minimum of 1 prior therapy; however, there are no minimum systemic therapy requirements for well differentiated or de-differentiated liposarcoma, clear cell sarcoma, chondrosarcoma, alveolar soft part sarcoma and chordomas which have no effective therapies; for Phase Ib, there are no maximum limits to number of prior therapies; for Phase II, there is a maximum of 5 prior chemotherapy regimens including tyrosine kinase inhibitors (TKI); the last dose of systemic therapy (including TKI) must have been given at least 2 weeks prior to initiation of therapy; patients receiving nitrosurea (such as BCNU) or mitomycin C must have received their last dose of such therapy at least 6 weeks prior to initiation of therapy; patients receiving bevacizumab must wait at least 4 weeks; patients receiving experimental immunotherapy or antibody based therapies must wait a minimum of 4 weeks or 4 half-lives, whichever is longer; this should be discussed with the Principal Investigator before registration; tumor biopsies should be performed only after meeting these requirements; patients should recover to less than Common Terminology Criteria for Adverse Events (CTCAE) grade 2 toxicities related to previous therapies to be eligible; patients with metastatic or locally advanced (inoperable) gastrointestinal stromal tumor (GIST) must have progressed on imatinib and sunitinib or be intolerant to both drugs; the last dose of tyrosine kinase inhibitors imatinib or sunitinib should be given at least 2 weeks prior to initiation of therapy; patients with brain metastasis that have been treated with definitive surgery or radiation and have been clinically stable for 3 months following the procedure with no neurological signs or symptoms and no requirement for systemic glucocorticoids are eligible for study.

Condition	Intervention
Dermatofibrosarcoma Protuberans	**Drug:** vismodegib
Study ID Numbers: NCI-2011-01412, NCI-2011-01412, CDR0000680558, MSKCC-10049, 10-049, 8406, P30CA008748, U01CA069856 **ClinicalTrials.gov Identifier:** NCT01154452	