Phase II Trial Evaluating Resection Followed by Adjuvant Radiation Therapy (RT) for Patients with Desmoplastic Melanoma

**Purpose of Study:**

- **Primary Goals:**
  1) Assess the recurrence rates in patients with Desmoplastic Melanoma (DM) greater than or equal to 1 mm deep treated with adjuvant radiotherapy after surgical resection.
  2) Assess recurrence rates in patients with locally recurrent DM treated with adjuvant radiotherapy after surgical resection.

- **Secondary Goals:**
  1) Evaluate the impact of adjuvant radiation therapy after surgical resection on disease free and overall survival.
  2) Evaluate the immediate and long-term morbidity of the addition of radiotherapy surgery.

**Study Chairs:**
Barbara Anamarie Pockaj M.D.
Richard L. Deming M.D.

**QC Specialist:**
Butch K. Kvittem CCRP

**Statistician:**
Jake B. Allred M.S.

**Nurse Resource:**
Evie Brennan R.N., B.S.N., O.C.N.

**Status:**
07/11/2003  Activated

**Projected Number of Patients:**
60

**Excluded:**
None

**Final Accrual:**
NA

**Stratification:**
None

**Schema:**
Registration
Radiation therapy

**Treating Schedule:**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Dose</th>
<th>Days</th>
<th>FX/Day</th>
<th>FX/Size</th>
<th># FX</th>
<th>RT Length</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 Gy</td>
<td>Twice a week (Monday and Thursday or Tuesday and Friday)</td>
<td>6 Gy</td>
<td>5</td>
<td>2.5 weeks</td>
<td></td>
</tr>
</tbody>
</table>

**Accrual:**
This study opened on July 11, 2003 and has accrued 15 eligible patients thus far. Eight are white males and Seven are white females. All 15 patients have desmoplastic melanoma classified as >=1 mm deep.
Adverse Events:  As of February 4, 2008, there was adverse event data available on 14 patients. There was 1 grade 3 adverse event which was pruritis, which was deemed not related to study treatment. Additionally the following grade 2 adverse events were reported: dermatitis-RT (3 patients, 2 definitely related, 1 probably related), fatigue (1 patient, definitely related), pain-RT (1 patient, definitely related), and alopecia (1 patient, not related).

Study Status:  This trial was opened to NCCTG on July 11, 2003 with an expected accrual of 60 patients. Fifteen patients have been accrued thus far, one patients have accrued in the last 6 months.
A Phase II Study of Temozolomide and Everolimus (RAD001) Therapy for Metastatic Melanoma

**Purpose of Study:**
1) To estimate the 9-week progression-free survival rate for patients diagnosed with stage IV malignant melanoma treated with a regimen of everolimus and temozolomide.

- **Secondary Goals**
1) To evaluate overall survival (OS) time and time to disease progression.
2) To assess the toxicity profile of the combination of RAD001 and TMZ when used to treat patients with stage IV malignant melanoma.
3) To assess clinical benefit rates (i.e., stable disease, partial remission and complete response rates).
4) To describe the impact of therapy on parameters of angiogenesis and immunity (systemic and tumor microenvironment).

---

**Study Chairs:** Svetomir Nenad Markovic M.D.  
Domingo G. Perez M.D.

**QC Specialist:** Carla R. Hilton

**Statistician:** Jake B. Allred M.S.

**Nurse Resource:** Evie Brennan R.N., B.S.N., O.C.N.

**Status:** 01/18/2008 Activated

**Projected Number of Patients:** 43

**Excluded:** None

**Final Accrual:** NA

**Stratification** None

**Schema:** Registation  
RAD001 + TMZ

### Treating Schedule:

<table>
<thead>
<tr>
<th>Arm</th>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
<th>Freq</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Everolimus (RAD001)*</td>
<td>10 mg/day</td>
<td>Oral</td>
<td>Days 1-5, 8-12, 15-19, 22-26, 29-33+</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>5HT3 inhibitor (Pre-treatment for Temozolomide)</td>
<td>See Section 9.2</td>
<td>Oral</td>
<td>See Section 9.2</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Temozolomide**</td>
<td>200 mg/m2/day</td>
<td>Oral</td>
<td>Days 8-12++</td>
<td></td>
</tr>
</tbody>
</table>

*Tablets should be taken once daily, preferably at night, with a glass of water one hour before or after food. Patients should avoid taking this medication with high fat content foods and refrain from eating fatty foods 2 hours before and 2 hours after administration of
everolimus (RAD001).

**Capsules should be taken once daily, preferably before bed, with a
glass of water one hour before or after food.

+All Subsequent Cycles (Cycles 2+): Days 1-5, 8-12, 15-19, 22-26.
++All Subsequent Cycles (Cycles 2+): Days 1-5, repeat every 28 days

**Study Design:** This protocol will assess the efficacy of temozolomide and everolimus in patients with metastatic melanoma using a one-stage phase II study design. The primary endpoint of this trial is to estimate the 9-week progression-free survival (PFS) rate. A patient will be considered a success if they are progression-free at the evaluation at the end of cycle 2 (approximately 9 weeks from registration). All patients who meet the eligibility criteria, sign a consent form, and start treatment will be included in the evaluation of the 9-week PFS rate (evaluable patients). The 9-week PFS was chosen in view of the schedule used in the first cycle (5 weeks of therapy); which would result in the first evaluation of tumor status being performed at 9 weeks (prior to starting the 3rd cycle).

A Phase II clinical trial comparing the impact of temozolomide to DTIC in the treatment of patients with advanced metastatic melanoma (Middleton, Grob et al. 2000), reported that the 9-week PFS rate was 35% with temozolomide alone and 30% with DTIC. We would consider recommending the combination of everolimus and temozolomide for further study if the proportion of patients who are progression-free at 9 weeks post-registration is at least 55%. Thus, for patients with stage IV malignant melanoma who are treated with the combination of temozolomide and everolimus we are interested in testing the hypothesis that the true PFS rate at 9 weeks is at most 35% against the alternative hypothesis that the true PFS rate at 9 weeks is at least 55%. To test this hypothesis, 39 evaluable patients will be analyzed. If at least 18 of the first 39 are successes, we will consider the regimen to be worth further study. Otherwise, this regimen will be considered ineffective in this patient population.

**Accrual:** As of February 4, 2008, 2 patients have enrolled into this study.

**Adverse Events:** Adverse event data on the 2 enrolled patients is not available at this time.

**Accrual Table:**

<table>
<thead>
<tr>
<th>Randomizing Membership</th>
<th>Total Entered</th>
<th>Past 6 Months</th>
<th>Past 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total Membership Accrual</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Trial ID</td>
<td>Trial Title</td>
<td>Status</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>947851</td>
<td>Phase II Trial of Fludarabine and Sandostatin LAR Depot for Relapsed Low-Grade Non-Hodgkin's Lymphoma</td>
<td>Closed: 04/28/2000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The manuscript for this trial is currently being written.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>948151</td>
<td>Phase II Trial of Long-Term Tamoxifen in Patients with Asymptomatic B-Cell Chronic Lymphocytic Leukemia</td>
<td>Closed: 07/31/1996</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A manuscript for this study is in preparation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>958053</td>
<td>A Phase II Trial of 2-CDA in Previously Treated or Untreated Patients with Mantle Cell Lymphoma</td>
<td>Closed: 03/17/2000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study results on previously untreated patients were presented at the 1999 ASH meeting. An ASH abstract on previously treated patients appeared in the 2001 NCCTG book.</td>
<td>Manuscript status: Manuscript has been accepted by Cancer.</td>
<td></td>
</tr>
<tr>
<td>978151</td>
<td>A Phase II Study of Alternating Cycles of Fludarabine and Cyclophosphamide in Previously Untreated Patients with B-Cell CLL</td>
<td>Closed: 10/09/2000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>One patient continues to be followed per protocol. The validity and accuracy of the data items are being checked, and a manuscript is in preparation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>988151</td>
<td>A Phase II Trial of Rituxan (C2B8) in Patients with Asymptomatic CD20+B-Cell Follicular Small Cleaved Low-Grade non-Hodgkin's Lymphoma or Relapsed CD20+ Hodgkin's Disease</td>
<td>Closed: 02/11/2000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Data for this study are being analyzed and a manuscript is currently being written.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>988152</td>
<td>Phase II Study of Gemcitabine for Relapsed B-Cell Chronic Lymphocytic Leukemia</td>
<td>Closed: 12/06/2002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The manuscript for this trial is currently being finalized.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N9981</td>
<td>A Phase II Trial of Cisplatinum, Cytosine Arabinoside, Dexamethasone (DHAP) With Rituxan in Patients With Relapsed CD20+ B-Cell Non-Hodgkins Lymphoma</td>
<td>Closed: 06/20/2003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study results were presented at the ASCO 2006 meetings.</td>
<td>The manuscript for this trial has been accepted for publication in</td>
<td></td>
</tr>
</tbody>
</table>
Leukemia and Lymphoma.

N9982  * A Pilot Study of Thalidomide as an Inhibitor of Angiogenesis in the Treatment of Myelofibrosis with Myeloid Metaplasia (MMM)
* Closed: 04/18/2003
* The quality and accuracy of the data are being validated and a manuscript is in preparation.

N9986  * A Phase II Trial of Thalidomide in Patients with Relapsed Chronic Lymphocytic Leukemia
* Closed: 08/15/2003
* Manuscript is in preparation.

N998B  * A Phase II Study of Thalidomide in the Treatment of Myelodysplastic Syndromes in Adults: A Clinical and Biologic Study
* Closed: 03/08/2002
* A manuscript on this trial has been published in Cancer:
N0782  Changes in BLyS and Other Cytokines After Rituximab Treatment

**Purpose of Study:**
1) Determine the serum levels of BLyS and other cytokines in follicular lymphoma patients treated with 4 doses of Rituximab both at baseline and after 4 months.
2) Correlate the cytokine changes with clinical endpoints such as response to treatment and time to progression.

**Schema:** No Schema Defined

******************************************************************************

N0775  A Randomized Phase II Trial of Temozolomide (TMZ) and Bevacizumab or ABI-007 (ABX)/Carboplatin (CBDCA) and Bevacizumab in Patients with Unresectable Stage IV Malignant Melanoma

**Purpose of Study:**
- **Primary Goal**
  1) To assess the anti-tumor activity in terms of the percentage of patients who are progression-free at 6 months and safety profile of each of the treatment regimens.
- **Secondary Goals**
  1) To estimate the response rate in each of the treatment regimens.
  2) To estimate the distribution of PFS times and OS time of each treatment regimen.

**Schema:** Randomize
- Arm A (Temozolomide + Bevacizumab)
- Arm B (Bevacizumab + ABI-007 + CBDCA)

******************************************************************************

E1F05  Phase II Study of Rituximab Given in Conjunction with Standard Chemotherapy in Primary Central Nervous System (CNS) Lymphoma

**Schema:** Randomize
- Arm A (Temozolomide + Bevacizumab)
- Arm B (Bevacizumab + ABI-007 + CBDCA)