NCCTG Status Report for Study N0275 – May 2011

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) >1mm deep 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 to surgery.

Design Schema:
Registration
Radiation therapy

Study Chair:
Barbara A. Pockaj, M.D.
Richard L. Deming, M.D.

Statistician: Jake Allred, M.S.

Projected Number of Patients: 60

Treating Schedule:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Days</th>
<th>FX/Size</th>
<th>#FX</th>
<th>RT Length</th>
</tr>
</thead>
<tbody>
<tr>
<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>
</tr>
</tbody>
</table>

Study Design:

Forty patients with DM ≥1mm deep will be accrued and treated with adjuvant radiotherapy after surgical resection. Similarly, 20 patients with locally recurrent DM will be accrued at treated with adjuvant radiotherapy after surgical resection. Data will be used to calculate 95% confidence intervals for the true 2 year local recurrence rate in each group.

Study Status/Accrual:

This study was opened on 07/11/2003 and was closed on 07/31/2009 with a final accrual of 20 patients.
Adverse Events:

There is adverse event data available on all 20 patients. There has been one patient with grade 5 cardiovascular that was not related to study treatment. There has been 3 grade 3 adverse events; pruritis, prothrombin time and hyponatremia (all of which were deemed not related to study treatment). See Table 1.

Table 1: Adverse Event Summary

**Protocol N0275 - Resection RT Melanoma**

**Adverse Events (Regardless of Attribution)**

**Arm A Evaluable Patients: 20**

<table>
<thead>
<tr>
<th>Patients with at least one:</th>
<th>Arm</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3+ Adverse Event</td>
<td>A</td>
<td>4</td>
<td>20.0</td>
</tr>
<tr>
<td>Grade 4+ Adverse Event</td>
<td>A</td>
<td>1</td>
<td>5.0</td>
</tr>
<tr>
<td>Grade 3+ Non-Hem Adverse Event</td>
<td>A</td>
<td>4</td>
<td>20.0</td>
</tr>
<tr>
<td>Grade 4+ Non-Hem Adverse Event</td>
<td>A</td>
<td>1</td>
<td>5.0</td>
</tr>
</tbody>
</table>

**Protocol N0275 - Resection RT Melanoma**

**Adverse Events For All Patients (Regardless of Attribution)**

**Arm A Evaluable Patients: 20**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Type</td>
<td>Arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DERMATITIS-RT</td>
<td>A</td>
<td>15</td>
<td>75.0</td>
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<tr>
<td>PAIN-RT</td>
<td>A</td>
<td>4</td>
<td>20.0</td>
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<tr>
<td>ALOPECIA</td>
<td>A</td>
<td>3</td>
<td>15.0</td>
</tr>
<tr>
<td>ANOREXIA</td>
<td>A</td>
<td>3</td>
<td>15.0</td>
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<tr>
<td>DYSPHAGIA</td>
<td>A</td>
<td>2</td>
<td>10.0</td>
</tr>
<tr>
<td>CARDIOVASCULAR</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYPOATREMIA</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROTHROMBIN TIME</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRURITIS</td>
<td>A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Phase II Study of Temozolomide and Everolimus (RAD001) Therapy for Metastatic Melanoma

Purpose of Study:

Primary
- 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
- Evaluate overall survival (OS) time.
- Evaluate time to disease progression.
- To assess the toxicity profile of the combination of everolimus and temozolomide when used to treat patients with stage IV malignant melanoma.
- To assess clinical benefit rates (i.e., stable disease, partial remission and complete response rates).

Translational
Describe the impact of therapy on parameters of angiogenesis and immunity (systemic and tumor microenvironment).

Study Status/Accrual:

This study was opened on 01/18/2008 and was closed on 10/03/2008 with a final accrual of 49 patients. There was 1 patient deemed ineligible.

The final complete Status Report was produced Spring, 2010.

References:

Abstract:

Background: A recently described escape mechanism of melanoma cells exposed to alkylating agents is the production of the pro-survival cytokine vascular endothelial growth factor (VEGF). We hypothesized that the combination of TMZ and RAD001 could provide an additive therapeutic benefit in metastatic melanoma and impact the antitumor immune response due to the effect of both agents on immune cell function. Methods: We conducted a single arm phase II trial of the combination of RAD001 (10 mg/day for 5 of 7 days) and TMZ (200 mg/m² days 1-5 every 28 days) in patients with stage IV unresectable MM. Patients (pts) began therapy with RAD001 1 week before initiation of TMZ (cycle 1 = 5 weeks, other cycles = 4 weeks). Pts previously treated with systemic therapy (excluding study agents) were eligible. Major exclusion criteria were active brain metastases, abnormal liver/renal function,
and poor performance status (PS > 2). The primary end point was 9 week progression free survival (PFS9) rate. With a sample size of 39, the one-stage study design had a significance level of 0.10 and 90% power to test the hypothesis that the true PFS9 rate is at most 35% vs the alternative of at least 55%. Regimen is considered promising if > 17 patients were PFS9 successes. Secondary end points included therapy associated changes of biomarkers of angiogenesis and immunity. **Results:** The study accrued 49 pts (1 ineligible) from 01/08-10/08 (median age: 60 years [range 28-84]). The most common metastatic sites were lungs (43%) followed by lymph nodes (28%) and liver (20%), with 27% of patients having prior chemotherapy. Of the first 39 evaluable pts, 17 (44%, 95% CI: 28-60%) were PFS9 successes. Overall 4 of 48 (8%) pts achieved a partial response, the median PFS was 2.4 months (95% CI: 2.1-4.0), and the median OS was 8.6 mos (95% CI: 7.1-12.2). Treatment was well tolerated, only 1 pt discontinued therapy due to toxicity (hyperlipidemia). Results of correlative laboratory studies are forthcoming. **Conclusions:** The combination of TMZ and RAD001 did not appear to offer a therapeutic advantage over TMZ-alone historic controls. Pending biomarker analysis may offer insights into potential combinations of the current regimen with other treatments in advanced melanoma.
A Randomized Phase II Trial of Temozolomide (TMZ) and Avastin® or ABI-007/Carboplatin (CBDCA) and Avastin® in Patients with Unresectable Stage IV Malignant Melanoma

Purpose of Study:

**Primary**
To assess the anti-tumor activity in terms of the percentage patients who are progression free at 6 months and safety profile of each treatment regimen.

**Secondary**
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.

**Translational**
To examine the impact of therapy on angiogenesis and immune homeostasis.

Study Status/ Accrual:
This study was opened on 09/19/2008 and was closed on 01/12/2010 with a final accrual of 86 patients.
The final complete Status Report was produced Spring 2010.

References:
Manuscript in progress.
NCCTG Status Report for Study N1085 –May 2011

A Phase I/II Study of Everolimus (RAD001) plus R-CHOP for New Untreated Diffuse Large B-Cell Lymphoma (DLBCL)

**Purpose of Study:**

**Primary**
- Phase I: To establish the maximum tolerated dose of RAD001 in combination with R-CHOP chemotherapy.
- Phase II: To assess the feasibility of RAD001 (everolimus) in combination with standard R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) in patients with newly diagnosed diffuse large B-cell lymphoma.

**Secondary**
- Phase I: To describe the toxicities associated with RAD001 in combination with R-CHOP chemotherapy.
- Phase II:
  1. To further describe the toxicities associated with RAD001 in combination with R-CHOP chemotherapy.
  2. To assess the rate of event-free survival at 12 months for diffuse large B-cell lymphoma patients treated with RAD001 in combination with R-CHOP chemotherapy.
  3. To evaluate overall response rate, complete response rate, duration of response, event-free survival, overall survival, and progression-free survival for patients treated with RAD001 in combination with R-CHOP chemotherapy.

**Correlative studies**

1. To profile gene expression using immunohistochemistry and categorize patients as germinal-center B-cell-like (GBC) vs. activated B-cell-like (ABC) vs. unclassified lymphoma subtype.
2. To determine whether previously identified predictive markers in large cell lymphoma remain valid with the addition of everolimus to R-CHOP chemotherapy.

**Design Schema:**

**Registration**
- Everolimus + RCHOP
Phase I/II Study of the Combination of Bendamustine, Rituximab and MK-2206 in the Treatment of Relapsed Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Purpose of Study:

1. Phase I: To assess the safety and maximum tolerated dose (MTD) of MK-2206 in combination therapy with bendamustine-rituximab in relapsed CLL or SLL patients.

2. Phase II: To assess the rate of complete response (CR) of MK-2206 in combination with bendamustine-rituximab in relapsed CLL or SLL patients.

3. To assess clinical efficacy of MK-2206 in combination with bendamustine-rituximab as demonstrated by analysis of overall response rate (CR, CRi, CCR, nPR and PR), duration of response, and treatment free survival.

4. To assess the toxicity profile of MK-2206 in combination with bendamustine-rituximab.

5. Evaluation of whether the established CLL prognostic factors (CD38, CD49d, IGHV, FISH and ZAP-70) predict responses to the combination therapy of MK2206, with bendamustine-rituximab.

6. Minimal residual disease will be evaluated after treatment in patients who achieve a clinical response. MRD status will be explored in relation to both the quality and duration of response.

7. Evaluation of the effects of the addition of MK-2206 to bendamustine-rituximab on B cell receptor initiated, PI3K/Akt downstream signal pathways, apoptosis analysis and leukemic cell activation status, as well as multiple cytokine profiles and key gene expression analysis with focus on leukemic cells.

8. Evaluation of MSC-CLL biology including the effects of the addition of MK-2206 to bendamustine-rituximab on CLL marrow stromal cell (MSC) proliferation, migration and cytokine production, as well as the adhesion capacity between MSC and leukemic cells.

Design Schema: Registration  \( \rightarrow \) MK2206+Bendamustine+Rituximab  \( \rightarrow \) Observation  \( \rightarrow \) Event Monitoring
NCCTG Status Report for Study N1088 – May 2011

A Pilot/Feasibility Phase I Study of Bendamustine, Rituximab and Lenalidomide in Patients with Refractory/Relapsed Indolent NHL

Purpose of Study:
Primary: To establish the maximum tolerated dose of lenalidomide in combination with BR chemotherapy.

Secondary
1. To evaluate the toxicity profile of lenalidomide in combination with BR chemotherapy.
2. To assess progression free survival.
3. To assess the overall and complete response rates of lenalidomide in combination with bendamustine and rituximab in patients with relapsed/refractory indolent NHL.

Correlative studies
1. Explore serum cytokine profile changes prior to and after treatment.
2. As part of ongoing research for NCCTG Hematology studies, we are banking paraffin-embedded tissue blocks/slides and blood products for future studies.

Design Schema:
Registration
Rituximab + Bendamustine + Lenalidomide
Effect of Vitamin D Replacement on Tumor Response and Survival Parameters for Vitamin D Insufficient Patients with Lymphoid Malignancies

Purpose of Study:
1. To test whether vitamin D replacement in vitamin D insufficient patients with early stage CLL being managed with observation can produce tumor responses and prolong TTT.
2. To learn if vitamin D replacement in vitamin D insufficient patients with newly diagnosed untreated aggressive NHL can improve the EFS and OS to be equivalent to that of a control population of vitamin D sufficient patients.

Correlative studies
1. To study vitamin D metabolism gene polymorphisms, immune effector cells (lymphocytes, monocytes), serum cytokines, and tumor cells from vitamin D insufficient and sufficient patients entered on these trials to learn the effects of vitamin D on both tumor cells and the patient's immune system.

Design
Registration

Schema:
Assess serum 25(OH)D at on-study
If < 25 ng/mL, then replace with vitamin D3 50,000 IU weekly
If ≥ 25 ng/mL, then observe
NCCTG Status Report for Study 978151 – May 2011

A Phase II Study of Alternating Cycles of Fludarabine and Cyclophosphamide in Previously Untreated Patients with B-Cell CLL

Purpose of Study:

1. To assess the rate and duration of complete and partial remission with the study treatment schedule.
2. To monitor and assess toxicity of this alternating regimen.
3. Utilize molecular genetic studies and flow cytometry on peripheral blood cells from patients receiving CR by conventional criteria.
4. To apply FISH techniques using probes to chromosomes 12 and 13 as prognostic factors for time-to-progression and overall survival.

Study Status/Accrual:

This study was opened on 08/13/1999 and was closed on 10/09/2000 with a final accrual of 34 patients. The final complete Status Report was produced Spring, 2003.

References:

Manuscript in progress.
A Pilot Study of Thalidomide as an Inhibitor of Angiogenesis in the Treatment of Myelofibrosis with Myeloid Metaplasia (MMM)

**Purpose of Study:**
1. To investigate whether thalidomide is an effective therapeutic agent in patients with MMM.
2. To assess the effects of thalidomide on the myelofibrotic stroma with respect to microvascular architecture and angiogenesis, collagen and reticulin deposition, and the expression of the mediating growth factors bFGF, TGF-β, and PDGF, and their respective receptors.

**Study Status/Accrual:**
This study was opened on 05/05/2000 and was closed on 04/18/2003 with a final accrual of 35 patients.
The final complete Status Report was produced Fall, 2004.

**References:**