

## **PROTOCOL SYNOPSIS – CIBMTR PROTOCOL # T00008**

### **Multicenter Phase II Study of Non-myeloablative Allogeneic Stem Cell Transplantation (NST) Using Matched Unrelated Donor for Metastatic Renal Cell Carcinoma**

**Study Chairperson:** Naoto T. Ueno, M.D., Ph.D.

#### **Study Design:**

This is a multi-stage phase II, multicenter, prospective study to assess the overall best response among subjects with metastatic RCC who underwent matched unrelated donor NST. After each stage of patients (e.g. after 15, 25, 35, and 50 patients total are enrolled) stopping rules based on best response of CR/CRU/PR as well as on treatment related mortality (TRM) will be applied. If the stopping rule is not triggered, additional subjects will be enrolled in the next stage. The maximum sample size is 50 subjects. Accrual will not stop while each stage of subjects are being followed up for these outcomes.

**Primary Objective:** To determine the incidence of the best attained tumor response of CR + CRU + PR within 6 months after matched unrelated donor (MUD) allogeneic NST in subjects diagnosed with metastatic Renal Cell Carcinoma

#### **Secondary Objectives:**

- 1) To determine overall survival after MUD allogeneic NST
- 2) To determine the rate of complete donor myeloid and lymphoid chimerism after MUD allogeneic NST
- 3) To determine the incidence and severity of acute and chronic graft-versus-host disease (GVHD) after MUD allogeneic (NST). Death without GVHD will be considered a competing risk for this event
- 4) To determine the incidence of treatment-related mortality. Progression will be considered a competing risk for this event
- 5) To assess cytotoxic T lymphocyte reactivity
  - To determine whether peptides derived from RCC antigen G250 and others can be used to elicit T cell immunity
  - To determine whether CTL elicited against these antigens can lyse primary RCC cells or RCC cell lines
  - To identify donor-derived anti-RCC T lymphocytes using MHC/peptide tetramer technology in the peripheral blood of both donors and recipients after transplant and in the tumor tissues of recipients, and correlate with clinical outcome
- 6) To assess antibodies activity against potential tumor antigenic peptides involved in graft-versus-RCC effect by probing sera using phage libraries, and identify antibodies that increase compared to pre-procedure or treatment levels and correlate with clinical response

**Eligibility:****Inclusion Criteria -**

1. Age 18 to 65
2. Diagnosis of metastatic RCC (stage IV disease) with predominant conventional (clear) cell type
3. Prior nephrectomy
4. Karnofsky performance status  $\geq 80$
5. Available HLA-matched (8/8, 7/8) unrelated donor (assessing high resolution typing at HLA A,B,C, DRB1)
6. At least one prior immunotherapy; or immunotherapy + chemotherapy; or targeted therapy for metastatic RCC
7. Serum creatinine  $\leq 2.0$  mg/dL
8. Serum bilirubin  $\leq 1.5$  mg/dL
9. ALT (SGPT) or AST  $\leq 3$  x upper limit of normal
10. Normal serum calcium
11. Serum LDH level  $\leq 1.5$  x upper limit of normal
12. Signed informed consent

**Exclusion Criteria -**

1. Prior history of allogeneic stem cell transplantation
2. A diagnosis of RCC with histology other than conventional (clear) cell type
3. History or presence of brain metastasis
4. Complete response after nephrectomy
5. Progressive disease with more than 50% increase in diameter of nodules in three months
6. Uncontrolled hypercalcemia
7. Active infection requiring systemic antibiotic therapy with antibacterial, antifungal, or antiviral agents (continued antibiotic therapy after signs/symptoms are resolved for  $>$  seven (7) days is not an exclusion)
8. HIV infection
9. Pregnant or lactating women
10. Severe, unstable or uncontrolled cardiac disease (e.g., arrhythmias or heart failure)
11. Severe, unstable or uncontrolled pulmonary disease

**Treatment Description:****Preparative regimen:**

- Fludarabine 25 mg/m<sup>2</sup> IV once a day x 5 days (-6,-5,-4,-3,-2)  
Melphalan 70 mg/m<sup>2</sup> IV once a day x 2 days (-3,-2)

**Donor Stem Cell Collection:**

Stem cells will be collected in accordance with NMDP Protocols, Standards, Policies and Procedures (located at <https://network.nmdp.org>.)

G-CSF-stimulated Donor peripheral blood progenitor cells (PBSC) is the preferred stem cell source with bone marrow (BM) being utilized only if:

- (1) the desired donor declines donation of PBSC or
- (2) is ineligible to donate PBSC or

(3) the PBSC collection is less than  $1.0 \times 10^6$  CD34+ cells/kg. With donor consent, BM will be requested for immediate BM harvest

If the PBSC collection is between  $1-2 \times 10^6$  CD34+ cells/kg, it is appropriate to inform the NMDP Search Coordinating Unit (SCU) for preliminary notification that supplemental stem cell collection may be requested later.

Delay in neutrophil recovery (an ANC < 500 at Day 28) would justify a request for supplemental PBSC or BM.

Donor Stem Cell Infusion: Stem cells will be infused on day 0

GVHD prophylaxis: Tacrolimus and methotrexate  $5 \text{ mg/m}^2$  IV day 1, 3, 6 and 11

Growth Factor: G-CSF

### Conditioning Regimen and GvHD Prophylaxis

Day	-6	-5	-4	-3	-2	-1	0	1	3	6	11	As Clinically Indicated
Fludarabine	✓	✓	✓	✓	✓							
Melphalan				✓	✓							
Stem cell infusion							✓					
Tacrolimus					✓ Continue as clinically indicated							
Methotrexate								✓	✓	✓	✓	
G-CSF <sup>1</sup>							✓ Continue until ANC of $> 1.0 \times 10^9/\text{L}$ is achieved 3 days in a row.					

<sup>1</sup> Begin G-CSF Day 0 or when ANC falls below  $0.5 \times 10^9/\text{L}$

### Planned Treatment of Residual Disease or Progressive Disease after Allogeneic Transplantation

#### **Post-transplant management of Immunosuppression between 1 and 3 months:**

##### If No Acute GvHD

- If in complete remission (CR), (CRU), or partial response (PR), continue immunosuppressive agents to 3 months post transplant, then taper over 2 months if response maintained
- If any residual, recurrent/ progressive disease (PD), observe clinically and continue immunosuppressive agents until 3 months post transplant. Then taper
- If overt PD with imminent danger to subjects (e.g., impending fractures, spinal cord compression, brain metastasis), subjects can be treated with radiation therapy or surgery

##### If Acute GvHD

- If GVHD, treat based on institutional guidelines

**Post-transplant management of Immunosuppression after 3 months:**

**If No GVHD**

- If CR, CRU, PR, or stable disease (SD), without GVHD, taper immunosuppressive agent over 2 months
- If PD without GVHD, taper immunosuppressive agents over 2 weeks. If subject continues to have PD without GVHD four (4) weeks after discontinuation of GVHD, consider DLI. Assess tumor response 4 to 6 weeks after each DLI

**If Active GVHD**

- If CR, CRU, PR, or SD with GVHD, continue immunosuppressive agent and treat GVHD based on institutional guidelines. Attempt to taper immunosuppressive agents as early as possible
- If PD with GVHD, treat GVHD based on institutional guidelines. Attempt to taper immunosuppressive agents as early as possible once GvHD resolved. *Avoid DLI or cytokine therapy (interferon alpha, interleukin-2). Further management per institutional guidelines or discuss with protocol chair.*

**Post Transplant Management of Immunosuppression based on RECIST Status**

		Months after transplant	1	2	3	4	5	Continue as clinically indicated
<b>No GVHD</b>	CR/CRU/PR/SD	Continue Immunosuppression			Taper to discontinuation			
	PD <sup>4</sup>	Continue Immunosuppression			Taper over 2 weeks	4 weeks after discontinuing, consider DLI <sup>2</sup>		
<b>Active GVHD<sup>1</sup></b>	CR/CRU/PR/SD	Continue Immunosuppression			Taper immunosuppressives as early as possible			✓
	PD <sup>4</sup>	Continue Immunosuppression			Taper immunosuppressives as early as possible. Avoid DLI/cytokine therapy <sup>3</sup>			✓

<sup>1</sup> Treat GVHD per institutional guideline  
<sup>2</sup>

Assess tumor response 4 to 6

weeks after each DLI

<sup>3</sup> e.g. interleukin-2, interferon-α.

<sup>4</sup> PD not responding to treatment, in imminent danger (e.g., impending fractures, spinal cord compression, brain metastasis), subjects can be treated with radiation therapy or surgery

**Management of mixed donor chimerism** (less than 50% donor T-cell chimerism from peripheral blood.)

No intervention is to be taken based on chimerism results at Day +30.

Based upon chimerism studies day 100 or later:

- If no prior GVHD and less than 50% donor chimerism, then taper and discontinue immunosuppressive agents and consider DLI.
- If active GVHD, continue to treat and manage GVHD based on institutional guidelines.
- If prior but currently controlled GVHD, taper and discontinue immunosuppressive agents as tolerated. If still less than 50% donor chimerism four weeks after discontinuing immunosuppressive agents, then consider DLI.

**Donor Lymphocyte Infusions (DLI):**

Subjects may receive DLI under the following conditions:

- 1) If progressive disease (PD) without active GVHD and immunosuppressive agents have been tapered and discontinued greater than four (4) weeks
- 2) If less than 50% donor chimerism without active GVHD and immunosuppressive agents have been discontinued greater than four (4) weeks

**Accrual Objective:** 50 Recipients total

**Accrual Period:** Estimated accrual period is three years

**Subject Follow-up Schedule**

Follow-up for two years post transplant for all living subjects is required. Restaging and assessment of response will be carried out at approximately 30 days, 100 days, 6 months and 12 months following transplant. Toxicity will be assessed every two weeks until day 100. After one year, follow up for all subjects will be for survival only. If a subject withdraws from or is taken off the study prior to one year post transplant, they will continue to be followed for adverse events up to one year and survival for two years.

**Study Duration:** Estimated duration of study to achieve primary and secondary endpoint(s), including any follow-up is approximately five years