SYNOPSIS

Final Clinical Study Report for Study CA184027

ABBREVIATED REPORT

TITLE OF STUDY: A Phase IB Safety and Dose-Assessment Study of Neoadjuvant Ipilimumab Monotherapy in Patients with Urothelial Carcinoma Undergoing Surgical Intervention.

INVESTIGATORS/STUDY CENTERS: Padmanee Sharma, MD, PhD; M D. Anderson Cancer Center, Houston, TX

PUBLICATIONS:
2) Chen H, Liakou CI, Kamat A, et al. Anti-CTLA-4 therapy results in higher CD4^+ICOS^hi T cell frequency and IFN-\(\gamma\) levels in both nonmalignant and malignant prostate tissues. Proc Natl Acad Sci USA, 2009; 106:2729-2734.

STUDY PERIOD: Study Initiation Date: 13-Mar-2007
Study Completion Date: 06-Oct-2009

INTRODUCTION: The purpose of this study was to evaluate the safety profile and to determine the favorable and tolerable dose (3 mg/kg or 10 mg/kg) of ipilimumab as a neoadjuvant monotherapy in urothelial carcinoma subjects, scheduled for surgery consisting of cystectomy and/or nephroureterectomy. An abbreviated study report has been prepared to report the results of this pilot study.

OBJECTIVES: The protocol-specified objectives include the following:

Primary Objective: To characterize the safety profile and serious drug related adverse events (AE) of two of the established doses of ipilimumab and select a favorable and tolerable dose as a neoadjuvant monotherapy for subjects with urothelial carcinoma undergoing surgical resection.
Secondary Objective(s):

To obtain an early gauge of anti-cancer immunological activity by evaluating blood and surgical specimens for evidence of post-treatment lymphocytic infiltration (e.g. presumed immune response) compared to pre-treatment blood and biopsy samples or control untreated, banked tumor tissues from comparable subjects.

- To perform immunohistochemistry (IHC) and fluorescence activated cell sorting (FACS) analyses on obtained samples for comparison of ratio and total numbers of effector CD4+, effector CD8+, and regulatory FOXP3+ T cell populations.
- To perform reverse transcription polymerase chain reaction (RT-PCR) and messenger ribonucleic acid (mRNA) analysis obtained from tumor tissues for identification and comparison of cytokines such as TNF-α, IFN-γ, GM-CSF, TGF-β, IL-10, and IL-6.
- To perform enzyme-linked immunosorbent assay (ELISA) and enzyme-linked immunosorbent spot (ELISPOT) analyses on obtained samples to characterize humoral and T cell responses to tumor antigens such as cancer-testis antigens.

METHODOLOGY:

This was an open-label neoadjuvant Phase Ib safety and dose assessment study in subjects with urothelial carcinoma who were scheduled to undergo surgery with cystectomy and/or nephroureterectomy. A maximum of 6 subjects were assigned per dose level (for a total of 12 subjects for the study) to determine the favorable and tolerable dose depending on the safety profiles observed.

This study was divided into three phases: the screening phase (Day -56 to Day 1), the treatment phase (Week 1 to Week 8 surgery), and the follow-up phase (Week 8 to Week 24).

Subjects who met the eligibility criteria entered the treatment phase. In the treatment phase, two dose levels (3 mg/kg and 10 mg/kg) were evaluated for their safety profile and AEs. In the initial dose level, a total of 6 subjects, with 3 subjects in a group, received a dose of 3 mg/kg of ipilimumab, at Week 1 and Week 4. These subjects were followed for safety assessments for 4 weeks after the second dose.

- If \( \leq \) 1 subject in the initial group of 3 experienced a \( \geq \) Grade 3 drug related AE then a subsequent group of 3 subjects at the same 3 mg/kg dose level was initiated.
- If \( \geq \) 2 subjects of the 6 subjects at the 3 mg/kg dose level experienced a \( \geq \) Grade 3 drug related AE, the second dose level of 10 mg/kg was not to be initiated and enrollment was planned to be closed.
- If \( \leq \) 1 subjects out of 6 experienced the drug related AE at the dose of 3 mg/kg of ipilimumab, the next dose level was initiated and a group of 3 subjects received a dose of 10 mg/kg at Week 1 and Week 4.
- If \( \leq \) 1 subject of the 3 subjects initially enrolled at the 10 mg/kg dose experienced a \( \geq \) Grade 3 drug related AE, then an additional 3 subjects were enrolled at the 10 mg/kg dose level.

In addition, the following stopping rules applied: if at any time during the study \( \geq \) 3 subjects, regardless of dose level, experienced a drug related Grade 4 AE or any drug related Grade 3 skin or gastrointestinal AE that did not respond to therapy, no more subjects were to be enrolled. Enrollment was to be stopped if a single case of bowel perforation was observed. However, the study was completed as none of the subjects experienced the above stated events. Once subjects received a maximum of two doses, they were to undergo surgery at Week 8.

In the follow-up phase, subjects were followed up with one visit at Week 12-16 and a final visit at Week 24.

The planned duration of study was approximately 18-24 months. Subjects in both dose levels underwent laboratory evaluations and procedures as outlined in protocol
NUMBER OF SUBJECTS (Planned and Analyzed): A total of 12 subjects were planned to be enrolled (6 subjects per dose level). However, 15 subjects were enrolled and 12 were assigned and treated (6 subjects per dose level).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:
Subjects greater than 18 years old with pathologic stage TaN0M0, TisN0M0, or T1N0M0 urothelial carcinoma scheduled for cystectomy and/or nephroureterectomy were enrolled. Additionally, subjects with T2N0M0 disease without lymphovascular invasion or micropapillary features on pathology, and who did not require neoadjuvant chemotherapy, were enrolled. Subjects with T2N0M0 or T3N0M0 disease who could not receive cisplatin-based neoadjuvant chemotherapy due to poor renal function, or who refused neoadjuvant chemotherapy, were also enrolled. All T2 and T3 subjects were also scheduled for cystectomy and/or nephroureterectomy.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT:
Ipilimumab (formerly referred to as MDX-010 [BMS-734016]) was supplied as a clear, colorless solution in a 50 mg/vial or 200 mg/vial (5 mg/mL). Ipilimumab was administered as a 90-minute intravenous (IV) infusion at a dose of 3 mg/kg or 10 mg/kg. Treatment was administered at Week 1 and Week 4.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT:
Not applicable

CRITERIA FOR EVALUATION:

Safety: Subjects were evaluated for safety if they received any treatment. Safety was evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3), based on AEs, physical examinations, and clinical laboratory assessments. Adverse events (AEs) of unknown etiology associated with study drug exposure and consistent with an immune phenomenon were defined as immune-related AEs (irAEs) and were analyzed as a separate category of treatment-related AEs.

Immunological response: Immunological response was evaluated using blood and surgical specimens as evidence of post-treatment lymphocytic infiltration as a gauge of anti-cancer immunological activity. The presence of an immunological activity signal indicated at least a 2-fold increase in the ratio of effector CD4+ and/or CD8+ T cells to regulatory T cells and/or at least a 2-fold increase in the total number of CD8+ T cells. Not all secondary objectives listed were analyzed for this study. The efficacy analyses was very limited as it was part of exploratory pilot study.

STATISTICAL CONSIDERATIONS:

Sample Size Determination: The maximum sample size was 12 subjects (6 for each dosage). There was no power consideration for the sample size determination.

Statistical Analysis: All recorded AEs were listed and tabulated by system organ class, preferred term and treatment. The presence of immunological activity signal was listed.

SUMMARY OF RESULTS:

Disposition and Baseline Demographic Characteristics:
A total of 15 subjects were enrolled in the study: 12 subjects were assigned and treated; 3 subjects were enrolled but not assigned (1 subject no longer met the study criteria and 2 subjects for other reasons). Of the 12 treated subjects, 10 (83.3%) subjects completed the study and 2 (16.6 %) subjects discontinued; 1 (8.3%) subject due to an AE, and 1 (8.3%) subject due to other reasons (refused surgery). The subject disposition is presented in Table 1.
### Table 1: Subject Disposition-All Treated Subjects

<table>
<thead>
<tr>
<th>Ipilimumab Dose levels</th>
<th>Number of subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>N</td>
<td>6</td>
</tr>
<tr>
<td>Treated</td>
<td>6(100.0)</td>
</tr>
<tr>
<td>Completed</td>
<td>6(100.0)</td>
</tr>
<tr>
<td>Off Treatment</td>
<td>6(100.0)</td>
</tr>
</tbody>
</table>

**Reason off treatment**
- Adverse Event: 0 (0%) 1(16.7) 1(8.3)
- Other: 0 (0%) 1(16.7) 1(8.3)

A total of 10 males (83.3%) and 2 females (16.7%), with a median age of 68.5 years (range: 55 to 76 years) participated in the study. Subjects were either white (83.3%) or Black/African American (16.7%), (Table 2).

### Table 2: Baseline Demographic Characteristics- All Treated Subjects

<table>
<thead>
<tr>
<th>Ipilimumab Dose levels</th>
<th>3 mg/kg</th>
<th>10 mg/kg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

**Age (years)**
- Median: 68.5 68.5 68.5
- Min-Max: 55.0-75.0 62.0-76.0 55.0-76.0

**Gender**
- Female, n (%): 0 2(33.3) 2(16.7)
- Male, n (%): 6(100.0) 4(66.7) 10(83.3)

**Race**
- Black/African American, n (%): 1(16.7) 1(16.7) 2(16.7)
- White, n (%): 5(83.3) 5(83.3) 10(83.3)

**Safety Results:**
There were no deaths reported during the study. Serious adverse events (SAEs) were reported for 5 (83.3%) subjects each in ipilimumab 3 mg/kg and 10 mg/kg dose levels. One (1, 16.6%) subject was discontinued due to AE (diarrhea) at the ipilimumab 10 mg/kg dose level. None were discontinued at the ipilimumab 3 mg/kg dose level. Immune related adverse events (irAE) were reported for 5 (83.3%) subjects and 6 (100%) subjects in the ipilimumab 3 mg/kg and 10 mg/kg dose levels respectively. Inflammatory events regardless of causality (IERC) were reported for 5 (83.3%) subjects and 6 (100%) subjects in the...
Ipilimumab 3 mg/kg and 10 mg/kg dose levels respectively. The overall safety summary results are presented in Table 3:

Table 3: Overall Safety Summary:-All Treated Subjects

<table>
<thead>
<tr>
<th>Ipilimumab Dose levels</th>
<th>3 mg/kg</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>At least one AE (any grade)</strong></td>
<td>6(100)</td>
<td>6(100)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>5(83.3)</td>
<td>6(100)</td>
</tr>
<tr>
<td><strong>At least one related AE (any grade)</strong></td>
<td>6(100)</td>
<td>6(100)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>1(16.7)</td>
<td>4(66.7)</td>
</tr>
<tr>
<td><strong>At least one SAE (any grade)</strong></td>
<td>5(83.3)</td>
<td>5(83.3)</td>
</tr>
<tr>
<td><strong>AE leading to discontinuation of study therapy</strong></td>
<td>0</td>
<td>1(16.7)</td>
</tr>
<tr>
<td><strong>Immune Related Adverse Events (irAEs) (any grade)</strong></td>
<td>5(83.3)</td>
<td>6(100)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>0</td>
<td>3(50.0)</td>
</tr>
<tr>
<td><strong>Inflammatory Events Regardless of Causality (IERCs) (any grade)</strong></td>
<td>5(83.3)</td>
<td>6(100)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>0</td>
<td>3(50.0)</td>
</tr>
</tbody>
</table>

**Immunogenicity Results:**
Serum samples were evaluated for the development of antibodies to ipilimumab (human anti-human antibodies [HAHA]). All samples were negative for the presence of anti-ipilimumab antibodies at all timepoints evaluated.

**Immunological Response Results:**
All subjects had immunological response (ie, at least a 2-fold increase in the ratio of effectors CD4+ and/or CD8 + T cells to regulatory and/or at least a 2-fold increase in the total number of CD8 + T cells) based on the Week 4 assessment.

**Pharmacokinetics Results:**
All subjects underwent pharmacokinetic (PK) sampling and samples were assayed. The PK parameters were not assessed for ipilimumab for this study report.

**Other Secondary Endpoint Results:**
The results of other secondary biomarker endpoints are described in the publications of this study.
CONCLUSIONS:

Safety: The safety of Ipilimumab (3 mg/kg or 10 mg/kg) as a neoadjuvant monotherapy for subjects with urothelial carcinoma undergoing surgical resection appeared to be consistent with the known safety profile of Ipilimumab with the skin and gastrointestinal being the most commonly affected organs. Furthermore, irAEs observed in this study were mostly reversible and manageable according to the available management guidelines.

Immunological Response Results: An immunological response signal was observed for all subjects.

DATE OF REPORT: 28-Sep-2010