

## Active Clinical Trials – June, 2010

### Breast Cancer

#### 1. R 706 - Trial Assigning Individualized Options for Treatment: The TAILORx Trial

- Attention is beginning to focus on who should not, rather than who should, receive chemotherapy. Clinical indicators have not been accurate enough. Gene expression profiling of human breast cancer has been shown to be potentially useful. The Oncotype DX 21-gene Breast Cancer Assay analyzes cancer related genes and determines a “recurrence score”. The Recurrence Score it derives is highly correlated with risk of distant recurrence in women with hormone receptor-positive lymph node negative breast cancer.
- In this trial, the Oncotype DX Breast Cancer Assay will be utilized to prospectively guide treatment decisions for low risk and high risk tumors. In addition, this trial will attempt to refine the precision of the test in individuals who have intermediate risk tumors.

#### 2. R 720 - Phase III Trial of Continuous Schedule Doxorubicin/Cyclophosphomide and G-CSF Vs. Q. 2 Week Schedule Doxorubicin/Cyclophosphomide, Followed by Paclitaxel Given Either Every 2 Weeks or Weekly for 12 Weeks as Post-Operative Adjuvant Therapy in Node-Positive or High-Risk Node-Negative Breast Cancer

- Although post-operative adjuvant chemotherapy reduces the risk of relapse and death for women with operable breast cancer, the optimal means of administering currently available agents have not been clearly

determined. While the investigation of novel agents should be pursued, meaningful advances in therapy may also come from studies of alternative dose schedules of agents of known utility.

- Doxorubicin and cyclophosphamide (known as AC) followed by paclitaxel (T) (regimen known as AC-T) is one of several “standard” regimens commonly employed in the United States. A recent large Phase III study in node positive breast cancer patients showed significant advantages of every 2 week therapy (using AC-T) over every 3 week therapy in overall survival and disease-free survival. Based upon those results, treatment with AC administered every 2 weeks with growth factor support (to decrease bone marrow side effects), followed by paclitaxel every 2 weeks with growth factor support, has been selected as the control arm of this trial. The other arms of this randomized trial will investigate additional modifications of the doses and schedules of A, C, and T in an effort to optimize the administration of these agents, and to investigate biologic hypotheses.

### **3. R 755 – A Randomized Double-Blind, Placebo-Controlled Study of Everolimus in Combination with Exemestane in the Treatment of Postmenopausal Women with Estrogen Receptor Positive, Locally Advanced or Metastatic Breast Cancer Who are Refractory to Letrozole or Anastrozole**

- There are currently no treatments specifically approved for postmenopausal women with ER positive breast cancer after recurrence or progression on a non steroidal aromatase inhibitor (letrozole or anastrozole). To date treatment of these patients remains an area of unmet medical need.

- Exemestane is an irreversible steroidal aromatase inactivator that has demonstrated efficacy in the treatment of postmenopausal patients with advanced breast cancer. It is indicated for adjuvant treatment of postmenopausal women with estrogen receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy.
- Everolimus acts as a signal transduction inhibitor. An important aspect of the anti-tumor effect of everolimus is its potential to act both on tumor cells directly to inhibit growth and indirectly by inhibiting angiogenesis and displaying anti-vascular properties. Everolimus and letrozole synergistically inhibit proliferation in breast cancer cells.

#### **4. R 766 - A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase 3 Study of Denosumab as Adjuvant Treatment for Women with Early-Stage Breast Cancer at High Risk of Recurrence**

- Denosumab inhibits the formation, activation, and survival of osteoclasts. Osteoclasts are a type of bone cell responsible for destruction of bone. Denosumab decreases bone destruction and increases bone mass, volume, and strength.
- Investigators hypothesize that denosumab may delay the development of clinical metastasis and disease recurrence in early-stage breast cancer.
- The purpose of this phase 3 study is to evaluate the ability of denosumab to prolong bone metastasis free-survival

and disease free-survival in breast cancer patients at high risk for disease recurrence, when combined with standard of care adjuvant/neoadjuvant cancer therapy.

## Colorectal Cancer

### **1. R 709 - A Randomized Phase III Study Comparing 5-FU, Leucovorin, and Oxaliplatin versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers**

- Patients with Stage II colon cancer carry a 20-25% risk of recurrence. There is a need to identify the subset of patients with stage II colon cancer who are at greatest risk to develop disease recurrence. Data collected by ECOG and others suggest that two groups of patients can be defined, high-risk versus low-risk, based on molecular markers. If these retrospective molecular observations hold true for patients with stage II colon cancer, it will be possible to more clearly define a low-risk group that would not require postoperative therapy. (Low-risk stage II patients would have a 5-year survival rate of 90%, high-risk 60%.)
- In this study, patients determined to be high-risk by the molecular analysis will receive chemotherapy +/- bevacizumab. Bevacizumab, an anti-VEGF monoclonal antibody, blocks the growth of cancer cells. Its antitumor effect is enhanced when combined with chemotherapy, even over that of chemotherapy alone. A phase II study of bevacizumab plus 5-FU/leucovorin in patients with metastatic colorectal cancer led to a 40% tumor response rate. Recently, 5-FU/leucovorin/oxaliplatin (FOLFOX) has been proven to provide greater disease-free survival than

5-FU/leucovorin alone as adjuvant therapy for patients with colon cancer. In this study, the investigators propose that adding bevacizumab to FOLFOX will maximize its effects for the high-risk stage II patient.

**2. R 760 A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Pegfilgrastim Administered to Subjects with Newly Diagnosed, Locally-Advanced or Metastatic Colorectal Cancer Treated with Bevacizumab and Either 5-Fluorouracil, Oxaplatin, Leucovorin (FOLFOX) or 5-fluorouracil, Irinotecan, Leucovorin (FOLFIRI)**

- Vascular endothelial growth factor (VEGF) is a critical mediator of tumor angiogenesis and VEGF has become an important target for anticancer therapeutics. Bevacizumab (Avastin), a recombinant humanized monoclonal antibody with a high-binding specificity for VEGF, prevents the interaction of VEGF with its receptors on vascular endothelial cells and thereby disrupts angiogenesis.
- Pegfilgrastim is a granulocyte colony stimulating factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia,
- The addition of bevacizumab to chemotherapy results in increased rates of neutropenia in each of the tumor types for which bevacizumab has an indication.
- This study will evaluate the efficacy of pegfilgrastim versus placebo in reducing the incidence of grade 3/4 febrile

neutropenia for subjects receiving bevacizumab and chemotherapy.

## Head and Neck Cancer

### 1. R 705 - A Randomized, Open-Label, Controlled, Phase II Trial of Combination Chemotherapy With or Without Panitumumab as First-Line Treatment of Subjects With Metastatic or Recurrent Head and Neck Cancer, and Cross-over-Second-Line Panitumumab Monotherapy of Subjects Who Fail the Combination Chemotherapy Only Arm

- The goal of treating patients with recurrent Head and Neck Cancer (HNC) is to relieve symptoms and to extend survival. Metastatic HNC is usually treated with systemic chemotherapy, which may consist of either single drugs or combinations. Historically, the most frequently used combination was cisplatin and 5-FU.
- Several newer chemotherapy agents have demonstrated response rates in metastatic throat cancer that are similar to or higher than those obtained with the standard cisplatin-5FU combination, i.e. docetaxel combined with cisplatin.
- Over-expression of Epidermal Growth Factor (EGFr) is associated with malignant transformation in a number of solid tumor types such as prostate, breast, colon, lung, ovary, kidney, and head and neck. Over-expression of EGFr in squamous cell carcinoma of the head and neck has been associated with increased risk of treatment failure.
- Panitumumab is a high affinity human monoclonal antibody directed against human EGFr. *In vivo* studies

have demonstrated that panitumumab prevents tumor formation and can induce eradication of established tumors in an orthotopic xenograft model of squamous cell carcinoma of the head and neck.

- This study is designed to estimate the effect of adding panitumumab, to docetaxel and cisplatin combination chemotherapy, on median progression-free-survival.

## Lymphoma

**R 739 - A Phase III Multicenter, Open-Label Study of Rituximab Faster Infusion Time in Patients With Previously Untreated Diffuse Large B-Cell or Follicular Non-Hodgkin's Lymphoma.**

- Data from investigator-sponsored, single-center studies, have demonstrated that faster infusions of rituximab appear to be generally well tolerated and feasible in patients with NHL.
- The primary endpoint of this study is the development of grade 3 or 4 infusion related toxicities in patients who receive rituximab by faster infusion in Cycle 2 and who did not experience a grade 3 or 4 infusion related adverse event during the rituximab infusion given at the standard rate in Cycle 1.

## Lung Cancer

1. **R 743 - Multicenter, Randomized, Double-blind, Phase III Trial to Investigate the Efficacy and Safety of Oral BIBF 1120 plus Standard Pemetrexed Therapy Compared to Placebo plus Standard Pemetrexed Therapy in Patients with Stage**

## **IIIB/IV or Recurrent Non Small Cell Lung Cancer After Failure of First Line Chemotherapy**

- Almost all patients with locally advanced and/or metastatic NSCLC relapse despite the availability of several drugs for second-line monotherapy after failure of first line therapy.
- For these patients, addition of BIBF 1120 could offer a new treatment option when administered in combination with standard chemotherapy for second line therapy.
- Angiogenesis is involved in tumor growth and development of metastases. Vascular endothelial growth factor and platelet-derived growth factor contribute substantially to tumor angiogenesis. BIBY 1120 is a potent inhibitor of both.

## **2. R 750 - A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term Safety and Efficacy of Darbepoetin Alfa Administered at 500 ug Once Every 3 Weeks in Anemic Subjects With Advanced Stage Non-small Cell Lung Cancer Receiving Multi-cycle Chemotherapy**

- Anemia frequently develops in patients with neoplastic disease. The severity of cancer associated anemia depends in part on the extent of the underlying neoplastic disease as well as the regimen of cytotoxic treatments administered.
- Symptoms of anemia may include fatigue, dyspnea on exertion, shortness of breath, decreased motivation, and impaired cognition and depression, with fatigue

affecting greater than 65% of patients during their chemotherapy treatments.

- In situations where rapid reversal of anemia is required RBC transfusion is indicated, although allogeneic blood product transfusion carries potential undesirable risks. As an alternative to blood product transfusion, erythropoiesis stimulating agents (ESAs) have been employed as a pharmacological measure to palliate and/or reverse the anemia associated with chemotherapy in non-emergent settings.
- Darbepoetin Alfa, manufactured by recombinant DNA technology, has been reported to have a longer mean residence time and a 3-fold longer serum half-life than recombinant human erythropoietin in both dialysis and cancer patients.

### **3. R 767 – A Randomized, Multicenter, Open-Label, Phase 3 Study of Gemcitabine-Cisplatin Chemotherapy Plus IMC-11F8 Versus Gemcitabine-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients With Squamous Stage IIIb or IV Non-Small Cell Lung Cancer (NSCLC)**

- Epidermal Growth Factor (EGF) is part of a complex network of growth factors and receptors that together help to modulate the growth of cells. EGF is released by cells, and then is picked up either by the cell itself, stimulating its own growth, or by neighboring cells, stimulating their ability to divide. Receptors on the surface of the cell bind to EGF and relay the signal inside. Dysregulation of signal transduction pathways, including overexpression of growth factor receptors, is one of the fundamental elements contributing to the growth and progression of many solid tumors.

- Many common human tumors express EGFR and increased EGFR expression is frequently associated with poor clinical prognosis.
- IMC-11F8 is an anti-EGFR antibody that attaches to the receptor on the surface of cells and blocks the growth factor receptor.
- Studies with cetuximab, another anti-EGFR antibody, have shown enhanced antitumor activity of chemotherapy in NSCLC.
- The primary objective of this study is to evaluate the overall survival in patients with squamous Stage IIIb or IV NSCLC treated with IMC-11F8 plus gemcitabine-cisplatin chemotherapy versus gemcitabine-cisplatin chemotherapy alone in the first-line metastatic setting.

**4. R 768 A Randomized, Multicenter, Open-Label Phase 3 Study of Pemetrexed-Cisplatin Chemotherapy Plus IMC=11F8 Versus Pemetrexed-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients With Nonsquamous Stage IIIb or IV Non-Small Cell Lung Cancer (NSCLC)**

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- Many common human tumors express EGFR and increased EGFR expression is frequently associated with poor clinical prognosis.
- IMC-11F8 is an anti-EGFR antibody that attaches to the receptor on the surface of cells and blocks the growth factor receptor.
- Studies with cetuximab, another anti-EGFR antibody, have shown enhanced antitumor activity of chemotherapy in NSCLC.
- Pemetrexed is a drug that blocks DNA synthesis and has shown strong activity in the treatment of NSCLC, with reduced toxicity compared to other available agents and with comparable clinical efficacy.
- Histologic analysis has shown that pemetrexed may offer additional benefit when administered specifically to patients with nonsquamous histologies.

## Renal Cancer

### **R 731 ASSURE: Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma**

- Renal cell cancer (kidney cancer) affects over 33,000 people per year. Patients with locally advanced renal cell cancer, including Stage II, III, and IVa, have 5-year survival rates of 65-80, 40-60, and 0-20 percent, respectively. Those who relapse usually succumb to

distant metastases as a consequence of the lack of useful agents against this cancer (including biologic agents such as IL-2 and Interferon), both as treatment and as adjuvant (after surgery) therapy. Adjuvant vaccine trials are ongoing.

- Two promising oral targeted therapies have recently been described in patients with advanced disease. Sorafenib (BAY 43-9006), in a Phase III trial in advanced pre-treated renal cell cancer, produced a median disease-progression-free survival of 24 weeks, compared to 12 weeks with placebo. Sunitinib (SU011248), in two Phase II trials in metastatic renal cell cancer, has produced a 40-44% tumor response rate, and median duration of response of 8.1-8.7 months. The great need for safe and effective adjuvant therapy of renal cell cancer prompts testing of these new agents, sunitinib and sorafenib, in this setting.

### **Chemotherapy Induced Nausea and Vomiting**

**R 761 - A Multicenter, Open-Label, Single-Arm Evaluation of Palonosetron for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Subjects Who Have Experienced CINV During the Previous Cycle of Low Emetogenic Chemotherapy (LEC).**

- Patients receiving LEC agents have a 10% to 30% probability of developing CINV without prophylaxis/ Current guidelines recommend one antiemetic agent for patients receiving LEC; however, there is a lack of evidence in the literature to support a selection of antiemetic therapy in this patient population.

- Palonosetron has demonstrated to be a safe and effective antiemetic in patients receiving moderate or high emetogenic chemotherapy, but has not been evaluated in patients receiving LEC.
- This study is designed to evaluate palonosetron in the prevention of CI{NV for subjects receiving a LEC agent.