Carolinas HealthCare System
*Levine Cancer Institute*

UPDATES IN CANCER FOR CLINICIANS

WINTER 2014

# Progress in Hematologic Cell Transplantation

**Edward Copelan,** MD, *(left)*
*Chair of the Department of Hematologic Oncology and Blood Disorders*

**Belinda Avalos,** MD *(right)*
*Vice Chair of the Department of Hematologic Oncology and Blood Disorders*

Initial studies demonstrating a cure of acute leukemia with allogeneic transplantation were conducted by Nobel Laureate E. Donnall Thomas. Total body irradiation (TBI) with cyclophosphamide as preparative therapy was used.

This regimen has remained the standard for 50 years. Regimens substituting busulfan for irradiation have been used at many centers because of the relative ease of administration and lower rates of some delayed effects, including hypothyroidism, infertility and certain second malignancies. In randomized studies, however, TBI has been associated with lower rates of relapse in acute myeloid leukemia and better overall outcomes. These studies utilized fixed oral doses of busulfan, which is associated with up to twentyfold variations in plasma levels. Low plasma levels are associated with graft rejection and leukemia relapse and high levels with toxicity and transplant-related mortality. Improved methods of administration, including the intravenous route and dose adjustment of busulfan based on plasma levels, represent important advances which result in much less variation in plasma levels and less toxicity. Drs. Copelan and Avalos pioneered the use of busulfan preparative regimens and advances in its administration. The principal investigators and lead authors of the plenary paper in the December 5th issue of *Blood*, describe for the first time the superiority of intravenous busulfan compared to TBI in a study of 1,230 patients from more than 100 institutions worldwide who reported to the Center for International Blood and Marrow Transplant Research with acute myeloid leukemia in first remission.[1]

With a median follow up of surviving patients exceeding five years, the non-relapse mortality of patients receiving IV busulfan (IV Bu) was only 12 percent at one year and 18 percent at five years, comparable to reports using allegedly safer reduced intensity regimens, and significantly better than the TBI group in the study. Survival and leukemia free survival (57 percent at five years for IV Bu) were significantly higher and late relapse significantly less frequent with IV Bu compared to TBI. A supportive prospective cohort study in patients with various diagnoses, including AML, and shorter follow up and an accompanying commentary by Richard Champlin, of MD Anderson, supported and applauded the results of the study reported by Drs. Copelan and Avalos. Dr. Champlin labeled the study the "answer to an age-old question." The results are viewed by most experts as practice-changing; in addition to ease of administration and fewer complications, non-relapse mortality, late relapse, leukemia-

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# Message from the President of Levine Cancer Institute

**Derek Raghavan,** MD, PhD
*President, Levine Cancer Institute*

There is no question that every patient, caregiver and health professional will increasingly become involved in the "business" of healthcare in 2014. It's a pity, in one sense, as a great deal of time will be taken up by this topic, at the expense of time expended in cancer care and research. Some of the current and emerging chaos is clearly a problem of politics, with both sides of the houses of government, both federal and state, failing to execute complete and fiscally justified plans for healthcare coverage and reimbursement. The schism between federal and state policies is particularly problematic in North Carolina.[1] That said, it's time for our nation to focus on costs and quality of cancer care, leading to increased value for both patients and the community. I appreciate the view of Professor Michael Porter, from Harvard School of Business, who defines "value" as "outcome divided by cost," linking two very important parameters.[2]

The whole basis of developing Levine Cancer Institute has been to improve value – as outlined in my recent editorial in "Seminars in Oncology"[3], our approach has been to use electronically driven pathways to rationalize and refine care, focusing on using the most effective anti-cancer agents, and choosing less toxic options when the efficacies of different approaches are the same. Where approaches are equivalent in anti-cancer efficacy and toxicity, our intent is to move to a cost-based algorithm. We also are improving value by developing system-wide resources, such as availability of patient navigation, patient support teams, survivorship activities, e-genetic counseling, cancer trials, units to support patients at home and improved oncology palliative medicine. In this fashion, we can structure our System's approach to patient care, and base our decision process on the best available evidence and outcomes.

Similarly, we are focusing on value in our academic activities. I have participated actively in the writing of the ASCO Guidelines on Choosing Wisely, published in the *Journal of Clinical Oncology*[4, 5], and in helping to produce the recent NCI-ASCO position paper on making trials more accessible to the community and especially to under-served populations, published in *Journal of Oncology Practice*.[6] In addition, our Chair of Solid Tumor Oncology and Investigational Therapeutics, Ed Kim, MD, has recently produced a provocative manuscript on treatment selection and value in the management of lung cancer, in yet another high-tier journal.[7] Not to be outdone, the leaders of our Department of Hematologic Oncology, Blood Disorders and Bone Marrow Transplantation, Ed Copelan, MD, and Belinda Avalos, MD, have summarized their data on a new, more cost-effective approach to bone marrow transplantation in 1,230 cases in *Blood*.[8]

If you asked any within our team, our focus remains quality and consistency, as supported by our recent score of the top 1 percent in the Press Ganey survey. However, it is increasingly clear that our nation simply cannot afford the current costs of healthcare, and we all need to focus on the provision of value in addition to volume. We need to look at the reported advances and ensure that they are real, and of true clinical relevance, and not merely the products of a statistical exercise that produces a mathematical result of little real importance. This edition of *Updates in Cancer for Clinicians* will illustrate how our team is approaching the whole issue of value in healthcare, as well as several other important game-changing initiatives. I hope you find it to be of interest. Let us know if you require reprints of any of our published work.

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*Sincerely,*

We welcome your feedback at levinecancerinstitute@CarolinasHealthCare.org and look forward to bringing you more news in the future!

# The SELECT Lung Cancer Study: What did we learn about cetuximab and chemotherapy in second line treatment?

**Edward S. Kim,** MD
*Chair of the Department of Solid Tumor Oncology and Investigational Therapeutics*

Targeted therapies have become incorporated into our daily practice and management of patients with lung cancer. The discoveries of epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations have transformed survival in approximately 20 percent of lung cancer patients. The number of available compounds which target these pathways continues to grow and currently includes gefitinib, erlotinib, and afatinib for patients with EGFR mutation-positive lung cancer. Crizotinib (approved), LDK378 (currently under investigation) and others are not far away for patients with ALK positive lung cancer. Other targets of interest include MET, Kras, T790 (EGFR), FGFR, anti-CTLA-4, anti-PD-1 and BRAF. There are multiple ongoing studies evaluating agents against these targets.

Bevacizumab is an example of a targeted agent that has demonstrated improved efficacy in combination with chemotherapy, but does not have a specific measured target. Whether bevacizumab works synergistically with chemotherapy or if there is a specific unknown biomarker is still unclear. Other VEGF targeted agents have not been able to demonstrate similar efficacy. Cetuximab, a monoclonal antibody targeting EGFR, is FDA approved for the treatment of head and neck cancer and colorectal cancer. Kras has been identified as a marker of resistance against cetuximab in patients with colon cancer; however, no markers have been identified in head and neck cancer.

In lung cancer, cetuximab has been studied extensively. The FLEX study, a frontline advanced non-small cell lung cancer (NSCLC) trial combined with chemotherapy, showed a statistically significant improvement in overall survival (OS), however, this translated into only a five week difference.[1] The drug was not approved based on this information. Numerous biomarkers had been investigated to identify those patients that may benefit from cetuximab treatment including Kras, EGFR (expression, FISH), and others. A subset of patients from the FLEX study showed that H-score predicted an improved overall survival of 12 months (95 percent CI: 10.2-15.2 months) compared to 9.6 months (95 percent CI: 7.6-10.6 months).[2]

We observed initial activity with a single arm study of docetaxel and cetuximab in previously treated lung cancer patients.[3] Efficacy was encouraging with a response rate (RR) of 20 percent (95 percent CI: 10.4-33.0 percent) and thus the SELECT study was developed. This randomized study enrolled more than 900 patients with previously treated NSCLC. Chemotherapy with pemetrexed or docetaxel with or without cetuximab was utilized. Unfortunately, no significant improvements in efficacy were observed. We also tested H-score in this population and also did not observe a benefit in those patients testing positive.

Though these results were disappointing, definitive information will be gained from a current intergroup study, Southwest Oncology Group (SWOG) S0819, testing cetuximab with chemotherapy and bevacizumab. This is currently the largest front-line metastatic lung cancer study open to accrual (currently more than 1,000 patients on study) and was based on SWOG S0536, a single-arm, phase II study with promising efficacy using carboplatin, paclitaxel, bevacizumab, and cetuximab (OS: 15 months, RR: 56 percent).[4] Biomarker analyses are a co-primary endpoint with overall survival.

The need for additional treatments for lung cancer patients is paramount. However, the risk versus benefit of embarking on large phase III efforts needs to be based on solid, encouraging prior evidence. This leads to several questions: What parameters would best be used in order to test hypotheses in the current age of targeted therapy? Should a valid biomarker always be incorporated? Our hope is that a population of biomarker-enriched lung cancer patients who benefit from the S0819 regimen will be identified. Until we have this answer, higher levels of early phase data need to be generated in order to produce clinically meaningful endpoints in subsequent randomized studies and, for now, cetuximab appears to have a little role in non-small cell lung cancer.

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# Incorporating Palliative Care into Clinical Pathways


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In 2012, ASCO released a provisional clinical opinion stating that concurrent palliative care should be considered early in the course of advanced or metastatic cancer and/or in the setting of a high symptom burden.[1] This statement follows other organizational recommendations by the NCCN, Commission on Cancer, Institute of Medicine, European Society of Medical Oncology and the American Cancer Society, and was based on multiple randomized trials that reflect the benefit of early palliative care for improving patients' quality of life, patient and family satisfaction, decreased caregiver morbidity and decreased healthcare service utilization. Temel et al. demonstrated prolonged survival in the setting of metastatic non-small cell lung cancer (NSCLC) when palliative care is integrated at the time of diagnosis.[2]

Levine Cancer Institute supports full integration of palliative care into standard oncology care through development of its full-time outpatient clinic devoted to interdisciplinary palliative care. Additionally, palliative medicine has been incorporated into multiple evidence-based tumor-specific Levine Cancer Institute clinical pathways. Screening for palliative medicine referrals are recommended within Levine Cancer Institute's clinical pathways at the time of advanced disease in conjunction with ongoing disease specific treatments. Symptom management pathways were developed (locally) to guide oncology clinicians in providing primary palliative care in order to optimize symptom management along their patients' treatment course. These symptom management pathways are aimed at common distressing conditions encountered by individuals with cancer, including treatment-related side effects. When symptoms increase to a more challenging level of management, the pathways also provide guidance on when referral to a palliative medicine specialist should be considered. The symptom management pathways were created based on the medical evidence across the oncology and palliative medicine literature and are reviewed on a monthly basis at Levine Cancer Institute disease-specific section meetings. The symptom management pathways will evolve as new research is developed.[3]

At this year's American Academy of Hospice & Palliative Medicine's Annual Assembly, more than 2,400 medical providers convened to review the advancing role of palliative medicine within healthcare, across all care settings. Many studies and topics presented centered around the role of palliative medicine for patients with cancer. Specifically, topics including evidence-based symptom management for symptoms associated with cancer or its treatment, caregiver distress and support, survivorship needs, clinical trials and prognostication were highlighted throughout the assembly. However, the release

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# Progress in Hematologic Cell Transplantation *continued from page 1*

free survival and overall survival are all better with IV busulfan and cyclophosphamide than with TBI and cyclophosphamide. Additionally, the safety of this regimen is similar to that of reduced-intensity regimens that have less anti-leukemia activity. Busulfan in combination with TBI is the new standard preparative regimen for allogeneic transplantation in patients with acute myeloid leukemia.

The hematopoietic cell transplant team has incorporated these findings into its treatment protocols for the transplant program at Carolinas Medical Center, Charlotte, NC, with the new 16 bed unit opening January 22, 2014. The new unit provides positive pressure filtered air flow and other state-of-the-art protective environmental measures for patients with hematologic malignancies.

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## Palliative Medicine

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of the 3rd edition of the "Clinical Practice Guidelines for Quality Palliative Care" published by the National Consensus Project for Quality Palliative Care and authored by specialty pioneers Drs. Betty Ferrell and Diane Meier may have been the highlight for many palliative medicine teams.[4] These guidelines serve as principles for practicing the most effective and beneficial palliative medicine. Special emphasis is made on the necessity of interdisciplinary team members to provide evidence-based symptom management and holistic care that includes social, spiritual and ethical components. As the state of the science for palliative medicine continues to grow, it is imperative that teams across the country develop and grow their own interdisciplinary programs in conjunction with these guidelines, both of which are especially crucial for providing good patient care within cancer institutes.

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## The SELECT Lung Cancer Study: What did we learn about cetuximab and chemotherapy in second line treatment?

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# Stereotactic Radiation Approaches for Primary and Oligometastatic Malignancies

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When applied to therapeutic radiation, the term stereotactic refers to an extremely precise method of immobilization, imaging and targeting of a malignancy in order to maximize dose to the tumor while minimizing dose to surrounding normal tissues. First used to treat targets in the brain, using fixed head frames, the advent and integration of advanced imaging modalities and immobilization techniques in the treatment room have allowed this technology to be transported to the extracranial setting, where it is typically called stereotactic body radiotherapy (SBRT). Here, we offer a brief review of recent data and current trends in the field of stereotactic radiotherapy.

The role for SBRT is currently best established for patients with inoperable early-stage lung cancer, where prospective trials have demonstrated local control rates that rival surgical results. The most mature data comes from Radiation Therapy Oncology Group (RTOG) 0236, a phase II study of SBRT for patients with medically-inoperable stage I-II non-small cell lung cancer (NSCLC), which achieved an impressive two year local control rate of 93.7 percent.[1] Another recently completed phase II trial (RTOG 0618) evaluated SBRT as an alternative to surgery in patients with operable early stage NSCLC. At ASCO 2013, encouraging early results were presented, with a two year overall survival rate of 84.4 percent.[2]

Inspired in part by success in treating primary lung cancers, SBRT has also been recently used in the oligometastatic setting, where survival times are often significantly longer than for patients with frankly metastatic disease. As in the definitive setting, SBRT appears to be an effective and well-tolerated local therapy for patients with limited metastatic disease within the lung. Local control rates for lung metastases treated with SBRT have been reported as high as 94.7 percent.[3] In the liver, as well, SBRT is an attractive option for those not medically fit for hepatic metastasectomy; early studies have demonstrated local control rates of 92 percent.[4]

Intracranial stereotactic radiotherapy, termed stereotactic radiosurgery (SRS), has long been used to manage brain metastases, where it has proven worth as first line therapy, as postoperative therapy, and in combination with whole-brain radiation. Growing evidence also shows that radiosurgery to the resection cavity after resection of limited-brain metastases may be as effective as adjuvant whole-brain radiation therapy (the current standard). To that end, we also offer radiosurgery to an operable lesion either prior to planned surgical resection or after surgery to the resection bed as an alternative to whole brain radiation therapy. Our institutional experience with pre-operative SRS for cranial metastases is unique; our early results are promising, and will be published in the near future.

We have within Levine Cancer Institute an experienced stereotactic program for treatment of primary and metastatic tumors. In addition, there are many opportunities that the Levine Cancer Institute model provides for further developing this modality in a clinical research setting, and we are actively working towards this goal.

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FALL 2013

# Quality of Life Improvements in Sarcoma Therapy


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Levine Cancer Institute's multidisciplinary sarcoma team evaluates patients for current treatment options and novel research studies. However, a major consideration is the patient's quality of life. The two major drugs used for sarcoma therapy, doxorubicin and ifosfamide, can be given with increased safety and fewer side effects. After Europe, the Middle East and Africa banned use of dexrazoxane because of potential concern about increase in MDS in Europe, the Children's Oncology group did an analysis of more than 1,000 osteosarcoma patients treated in four studies. Lisa Kopp, MD, reported the results at the American Society of Clinical Oncology: development of MDS was very rare in this population and there were no increased events when comparing osteosarcoma patients who had received dexrazoxane before doxorubicin versus doxorubicin alone. Therefore, to reduce incidence of long-term cardiotoxicity, the use of dexrazoxane is not contraindicated. It is Dr. Anderson's opinion that benefit (less mucositis in the short term and less cardiotoxicity in the long term) outweighs any potential risk. For patients who have received more than 350 mg/m2 or have a more than 10 pecent decrease in EF, Dr. Anderson has safely used doxorubicin liposomes in both osteosarcoma and Ewing's sarcoma patients.

There is a new option to reduce mucositis: glutamine-disaccharide controlled (swish/swallow for 10 seconds). Dr. Anderson has published one pilot study, and two randomized placebo clinical trials, and designed a successful one in breast cancer patients, too. An improved glutamine disaccharide formulation (orange- or grape-flavored), now commercially available (healiosproducts.com), has trehalose in addition to sucrose to promote the entry (roughly 1,000 times greater) of the glutamine nutrient into mucosal cells.

Pazopanib, an oral drug for recurrent soft tissue sarcomas is now commercially available. The mechanism of action is VEGF inhibition. This drug is generally well tolerated at 800 mg per day. A common side effect is a salt and peppering or whitening of the hair. Fatigue can usually be managed by taking the drug at bedtime. Diarrhea and GI side effects, when they occur, are managed with loperamide.

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# Message from the President of Levine Cancer Institute

**Derek Raghavan,** MD, PhD
*President, Levine Cancer Institute*

We've been busy at Levine Cancer Institute, focusing on growth and review of progress. Carolinas HealthCare System was granted nursing Magnet status, and our team was delighted to be able to support our nursing leadership in the review process. Oncology nursing, and the certifications and responsibilities that go with this crucial discipline, are a huge part of Levine Cancer Institute's values, and it was exciting to the extramural validation. We were delighted that the Commission on Cancer reviewed seven of our programs and accorded us highest honors, with eight out of eight commendations.

We continue to recruit actively. Jon Gerber, MD, and Mike Grunwald, MD, have joined us from Johns Hopkins Cancer Center to expand the leukemia program, and Saad Usmani, MD, from Bart Barlogie's program at the University of Arkansas, now leads the myeloma program. Larry Druhan, PhD (Ohio State Comprehensive Cancer Center) and Sarah Baxter, PhD, (David Murdoch Research Institute) provide laboratory leadership in the Hematology Oncology Translational Labs. Jimmy Hwang, MD, has joined us from Georgetown University, where he was director of the Fellowship Program, to develop a Hematology and Oncology Fellowship, and to help lead in advanced upper gastro-intestinal cancers and phase I trials. Jai Patel, Pharm. D., has joined us from UNC Chapel Hill, to provide pharmacologic support for our early phase trials program. Leila Hadzikadic Gusic, MD, and Meg Forster, MD, surgical oncologists, from University of Pittsburgh Cancer Institute and the Moffitt Cancer Center, respectively will be helping develop our programs in breast cancer and upper gastro-intestinal cancer. Roshan Prabhu, MD, has joined the Levine Cancer Institute /SERO collaboration, coming from the very strong radiation oncology program at Emory University.

The Levine Cancer Institute External Advisory Board completed our first formal review in late July. This true blue ribbon panel includes:

- **Donald "Skip" Trump**, MD, President of Roswell Park Cancer Institute (chair)
- **John DiPersio**, MD, (chief, Hematologic Oncology and deputy director, Washington University Comprehensive Cancer Center)
- **Norm Hubbard**, PhD, (senior administrator, Seattle Cancer Care Alliance)
- **Fadlo Khuri**, MD, (chief of Medical Oncology, Emory University/Winship Cancer Institute
- **David Johnson**, MD, (chair of medicine, UT Southwestern and a former ASCO president), a member, but unable to attend this review
- **Mark Legnini**, PhD, (former leader of health policy and planning at Brookings Institute, now a consultant)
- **Debasish Roychowdhury**, MD, (chief medical officer, Sanofi Aventis)
- **Michael Steinberg**, MD, (chair, Radiation Oncology at UCLA and health consultant for many years to the Rand Corporation)
- **David Winchester**, MD, (surgical oncologist and medical director, American College of Surgeons Cancer Programs)

Their preliminary report indicates strong endorsement for our direction and aims, and the extraordinary progress over the past two years, with the addition of more than 80 faculty to Levine Cancer Institute.

As part of our quest for excellence, we also underwent a formal review of our Medical Physics program in Radiation Oncology, completed last month by Tim Fox, MD, (chief of Physics, Emory University) and Ping Xia, MD, (chief of Medical Physics, Cleveland Clinic Taussig Cancer Center). Their report is eagerly awaited.

We seem to be on track to develop a really unique resource for this region, providing better care and research for our patients, with a focus on innovation and support. This edition will tell you more.

*Sincerely,*

We welcome your feedback at levinecancerinstitute@carolinashealthcare.org and look forward to bringing you more news in the future!

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# State of the Art in Myeloma Management

**Saad Zafar Usmani,** MD, FACP
*Medical Oncology*

The management of multiple myeloma (MM) has seen a drastic change over the last 15 years, with the median survival for an average MM patient improving from more than 2 years to 7 to 10 years. MM represents a malignant clonal expansion of transformed plasma cells. These cells eventually undergo clonal evolution and heterogeneity, which is believed to be the basis of drug-resistance with sequencing therapy. This makes MM a complex, multi-hit malignancy with a prognosis and outcome that is extremely variable, even in the era of novel agents.

The initial prognostic models were developed based on clinical observations and routine laboratory findings. The most commonly used systems are International Staging System (ISS) and Durie-Salmon Staging (DSS), which includes data on the presence of bone lytic lesions, calcium, creatinine, albumin, b-2 microglobulin, hemoglobin concentration and serum levels of monoclonal proteins. Both these models provide an estimation of burden of disease and also capture host factors/morbidity, but do not account for the biologic heterogeneity of MM. Several techniques using comprehensive evaluation of bone marrow samples (metaphase cytogenetics, fluorescent in situ hybridization and gene expression profiling) have helped us identify the biologic bad actors in MM.

The eventual goal of prognostication for any human disease is to provide for risk-adaptive therapeutic strategy. Clinicians and cancer researchers now recognize that such prognostication needs to include the host factors (age, co-morbidities and performance status), disease burden (ISS and/or DSS) and disease biology. MM researchers recognize that our ability to assess the depth of response, by way of following serum M proteins and/or bone marrow examinations, is inadequate. Inclusion of novel imaging (PET/CT) and specialized lab tests (DNA PCR and/or flow cytometry) to assess minimal residual disease are being included to assess better depth of response in clinical trials. We also recognize that we need to find a better answer for high-risk myeloma patients and develop new drug classes that can improve their outcomes.

Levine Cancer Institute's Plasma Cell Disorders program has opened its doors to patients at its administrative and research headquarters in Charlotte, NC. The program brings these advances in management to the MM patients being cared for in Carolinas HealthCare System. We intend to achieve this goal by establishing uniform practice guidelines which help the oncologists across the Institute's vast network of satellite sites in treating MM patients and have readily available access to expert opinion. The program also brings value to Carolinas HealthCare System communities by offering clinical trials with novel treatments for both newly diagnosed and previously treated MM patients.

# Novel Approaches for Bone Metastasis

**Hadley Sharp,** MD *(left)*
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**Derek McHaffie,** MD *(right)*
*Radiation Oncology*

Bone metastases are a common source of morbidity in patients with metastatic cancer. Disease involving the spine is of particular interest due to the risk of developing metastatic epidural spinal cord compression (MESCC). In addition, pain and structural instability can greatly compromise patient performance status. The management of spinal metastases presents a unique challenge, requiring a multidisciplinary approach. When evaluating metastatic involvement of the spine, one must consider current neurologic function, radiation sensitivity, mechanical stability and systemic disease characteristics [1]. Surgical resection followed by fractionated radiation is the standard of care for MESCC. However, the management of the non-compressive tumors, inoperable patients, previously irradiated lesions, or radioresistant histologies (sarcoma, renal cell carcinoma or melanoma) require a more variable approach. In all these settings, the proximity of tumor to the spinal cord makes delivering a tumor ablative dose while sparing adjacent neural tissues, a unique challenge.

Using stereotactic techniques and prior knowledge of the radiation tolerance of the spinal cord, experience with spinal SBRT has shown long-term local control of more than 90 percent, including favorable outcomes for radioresistant histologies. Common fractionation schemes include 6 to 30 Gy in 1 to 5 fractions. Multiple institutional studies suggest an SBRT approach is more effective than conventional doses in all but the most radiation-sensitive histologies (lymphoma, myeloma, germ cell tumors). Limitations of these studies include heterogeneity in patient characteristics, reported endpoints, and fractionation schemes, making it difficult to unify into concise treatment recommendations. RTOG 0631, recently opened at Levine Cancer Institute has initiated the phase III portion of the trial comparing SBRT to high dose conventional radiation for spinal metastases with a primary endpoint of pain control. Other areas of active investigation include defining the role of SBRT for inoperable spinal cord compressive lesions and residual disease post-operatively. Optimizing fractionation schemes to balance local control, pain response, and the risk of neurologic sequelae or post-treatment vertebral body fracture will be important moving forward [2]. At Levine Cancer Institute, we are participating in cooperative group studies and establishing multidisciplinary approaches to spinal tumors.

In patients with multifocal symptomatic bone metastasis, systemic Radiopharmaceuticals can be an effective pain control strategy. Agents such as Strontium89 and Samarium153-EDTMP, which decay through beta emission, have been shown to result in high rates of objective pain response [3]. Concerns regarding bone marrow suppression without demonstrated efficacy for endpoints beyond pain control have limited the broad implementation of these agents. In May, the FDA approved Radium 223 Dichloride, the first alpha particle emitting radiopharmaceutical, for use in patients with castrate-resistant metastatic prostate cancer (CRPC), with symptomatic bone disease and no visceral metastases, based upon the results of the phase III ALYSYMPCA trial [4]. This study randomized 921 CRPC patients, who were otherwise receiving the highest standard of care in a 2 to 1 fashion to Radium 223 versus placebo . The study showed improvements in the trial's primary end point of survival (14.9 months vs. 11.3 months; $P<0.001$) and time to skeletal-related events (15.6 months vs. 9.8 months; $P<0.001$). Furthermore, no clinically meaningful differences in the rate of grade 3 or 4 toxicities were observed between arms.

Radium 223 is incorporated into hydroxyapatite formation, preferentially at sites of increased bone turnover. Once deposited, it undergoes a series of alpha particle (two protons and two neutrons) emissions with a half-life of 11.6 days. An alpha particle has 7,300 times the mass of a beta particle, transferring much higher energy to the surrounding tissue and resulting in more potent anti-tumor effects via non-repairable double-stranded DNA breaks. As a result of their size, they also manifest increasing stopping power and shorter effective ranges at the target site compared to beta particles. For Radium 223 decay, the range is measured at less than 100 µm, minimizing bone marrow suppression. By comparison, therapeutic beta-emitters have a range of 2.5-7 mm. Based upon

CONTINUED ON PAGE 7

# Update in HPV-Related Head and Neck Cancers

**Michael Haake,** MD *(left)*
*Radiation Oncology*

**Zvonimir Milas,** MD *(left)*
*Surgical Oncology*

**Ed Kim,** MD
*Chair of the Department of Solid Tumor Oncology and Investigational Therapeutics*

The incidence of oropharyngeal (tonsil and base of tongue) squamous cell carcinoma (OPSCC) is rapidly increasing and is directly associated with the rising rates of human papilloma virus (HPV) infection. Fortunately, these patients with HPV-related OPSCC are generally younger and have significantly improved survival rates in comparison to those with smoking- and alcohol-induced carcinoma.

The goals of cure and quality of life are of equal and critical importance. To achieve these goals, it takes a comprehensive team approach. Surgery, chemotherapy and radiation therapy all serve vital roles in the treatment of OPSCC. Evaluation and treatment by oral medicine, speech therapy, and physical therapy are very important to minimize post-treatment sequela. Thus, a multidisciplinary evaluation by medical oncology, radiation oncology, and head and neck surgical oncology is necessary to chart the ideal treatment plan which is individualized for each patient and compliant with the standards of care.

Surgical intervention for OPSCC has changed over the years. Historically, oropharyngeal cancer was managed with open surgery and then followed by radiation therapy for advanced primary tumors or nodal disease. However, there was much morbidity incurred despite the good outcomes. Currently, many investigators and centers have moved towards organ preservation treatment. The currently accepted standard of care for most cases of OPSCC utilizes radiation therapy, with or without chemotherapy, as the primary treatment modality.

The surgical arm of treatment often has a diagnostic, therapeutic, and surveillance role. An exam under anesthesia with direct laryngoscopy and biopsy is critical for diagnostic purposes as well as evaluating the extent of disease for treatment planning. Early stage disease limited to the primary site may be amenable to surgical resection, resulting in the possibility of treatment de-escalation. Salvage surgery is also critical in those patients whose OPSCC is refractory to primary treatment or is recurrent after treatment. Finally, surveillance of treated patients requires both radiographic imaging as well as examination with office-based laryngoscopy.

Radiation techniques, such as Intensity Modulated Radiation Therapy (IMRT) allows true "dose painting" of the area at risk, as determined on the CT/PET. The planning software allows for setting dose constraints on normal tissue to minimize long term symptoms such as dry mouth, soft tissue fibrosis and scarring.

Chemotherapeutic approaches have included utilizing sequential induction chemotherapy at the same time as radiation, which has increased the control of cancers and the overall cure rate. Novel targeted agents, such as cetuximab and others, combined with radiation may hold even more promise with less toxicity. As noted above, people with HPV-related cancers of the oropharynx have a better prognosis. Research is ongoing at Levine Cancer Institute and elsewhere to determine if such patients can have de-escalation of their chemotherapy and radiotherapy and still get the same results.

Multimodality care of patients with OPSCC is critical for both curative purposes and functional outcomes. Current treatment outside of the research trial setting should still focus on standard therapy with multidisciplinary discussion prior to treatment initiation.

# Upper GI Malignancies

**Jimmy Hwang,** MD
*Medical Oncology*

Progress in the treatment of metastatic gastroesophageal cancers has been slow. In patients with HER-2 overexpressing/amplified disease, the ToGA study proved the addition of trastuzumab to cisplatin/fluoropyrimidine therapy improved survival (1). Since then, other molecularly-targeted therapies, including bevacizumab, cetuximab, panitumumab, and everolimus failed to show significant survival benefits in large randomized trials (2-5). 2013 has produced mixed results.

At the Gastrointestinal Cancer Symposium, Fuchs reported a phase III study in the second-line setting comparing ramucirumab (IMC 1121), a fully human monoclonal antibody targeting VEGF Receptor 2, to placebo (Table 1). Ramicirumab significantly improved survival, primarily by stabilizing disease, and was tolerable, about as anticipated with anti-VEGF monoclonal antibodies (6). Additional data from a parallel study of paclitaxel with or without ramucirumab is expected.

Hecht presented a phase III study evaluating lapatinib in HER-2 amplified metastatic gastroesophageal adenocarcinomas at the ASCO annual meeting (Table 2). Patients were randomized to oxaliplatin and capecitabine (850 mg/m2 BID D#1-14) every three weeks with either lapatinib 1250 mg daily, or placebo. Adding lapatinib to chemotherapy increased overall survival somewhat, but not significantly. However, lapatinib also increased toxicity, especially severe diarrhea and rash (7). Lapatinib may not have performed as expected because the greater toxicities that occurred in combination with chemotherapy may have resulted in lower dose intensity. Our future approaches will focus on innovative therapies that add both clinical relevance to statistical significance.

Optimism about the potential of targeted therapy in gastroesophageal cancer continues. Further exploration of HER-2 targeting therapies persists with pertuzumab (with trastuzumab), and ado-trastuzmab-emtansine (T-DM1), in the initial and second line settings respectively, based on their efficacy in breast cancer.

Immunotherapy, especially the PD-1 pathway, is an area of investigation in many malignancies, which may overexpress the ligands PDL-1 or PDL-2, thereby suppressing immune surveillance. Inhibiting interactions between PD-1 and its ligands, currently with antibodies, may help eradicate malignancy. Data from patients with gastric cancer suggests that targeting the PD-1 pathway is beneficial (8).

Another promising target is c-Met, a tyrosine kinase receptor activated by its ligand HGF

| | Chemotherapy/Lapatinib | Chemotherapy | Comment |
|---|---|---|---|
| Median Survival | 12.2 months | 10.5 months | HR=0.91 (P=0.35) |
| Median PFS | 6.0 months | 5.4 months | HR 0.82 (P=0.10) |
| Objective Response | 53% | 40% | |

TABLE 2: Capecitabine/Oxaliplatin with or without Lapatinib as First-Line Therapy in Metastatic Gastroesophageal Cancer (from Hecht et al, 7)

| | Ramucirumab | Placebo | Comment |
|---|---|---|---|
| Median Survival | 5.2 months | 3.8 months | HR 0.776 (P=0.0473) |
| 1-year Overall Survival | 18% | 11% | |
| Median PFS | 2.1 months | 1.3 months | HR=0.483 (P<0.0001) |
| 12 week PFS | 40% | 16% | |
| Objective Response Rate | 3.4% | 2.6% | |
| Disease Control Rate | 49% | 23% | P<0.0001 |

TABLE 1: Ramucirumab as Second-line therapy in Metastatic Gastroesophageal Cancer (From Fuchs et al, 6)

CONTINUED ON PAGE 7

## FLIMS Workshop Recap

**Kathryn F. Mileham,** MD
*Medical Oncology*

Kathryn R. Mileham, MD, Medical Oncologist at Levine Cancer Institute, part of Carolinas HealthCare System, was selected to attend the 15th annual Methods in Clinical Cancer Research Meeting in Flims, Switzerland. Dr. Mileham was one of five delegates from North America selected to attend this prestigious international workshop, which focuses on the development of protocols and translational research studies. Dr. Mileham's study proposal centered on targeting specific biomarker pathways in early stage lung cancer patients.

## Novel Approaches for Bone Metastasis

*continued from page 4*

the benefits and favorable side effect profile observed in this trial, expanded and evolving indications will likely be forthcoming.

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## Quality of Life Improvements in Sarcoma Therapy

*continued from page 1*

Ifosfamide+ mesna is a commonly used regimen for treatment of bone and soft tissue sarcomas. Dr. Anderson recently published stability results so pharmacies have information for prolonged seven- or 14-day infusions. The excellent stability of ifosfamide+ mesna at 20 mg/mL for seven and 14 days allows portable pumps and outpatient treatment. Use at Levine Children's Hospital and Levine Cancer Institute will involve rental/consignment of reliable pumps by InfuSystem. Oncology pharmacy will provide the mesna + ifosfamide in a 200-1000 mg bag to be carried in a backpack, handbag or other bag. This should offer an easy and reliable means to give ifosfamide/mesna to patients on an outpatient basis. The Infusystem is also useful for overnight mesna infusions after cyclophosphamide. Using this set up, both Levine Children's Hospital and Levine Cancer Institute can facilitate more outpatient-friendly sarcoma therapy.

Finally, there is a new targeted alpha-emitting radiopharmaceutical for bone metastases, radium-223. This drug (Xifigo) is FDA approved for prostate cancer, but should also become a useful adjunct in the treatment of osteosarcoma. The advantage of alpha emitters is low marrow toxicity and less likelihood of resistance, since the high energy charged alpha particles cause difficult-to-repair double strand breaks in cancer cells. Thus, axial or metastatic cases may have new and better means to facilitate control, with or without surgery or external beam radiotherapy. Since the radiopharmaceutical acts like calcium and is incorporated into new bone, the screening test is a routine bone scan to identify osteoblastic lesions amenable to this new alpha radiotherapy.

## Upper GI Malignancies

*continued from page 6*

(hepatocyte growth factor). About half of patients with gastroesophageal cancers express c-Met, making this is an attractive target (9). Onartuzumab (MetMAb), a monoclonal antibody targeting c-Met, is being evaluated in randomized studies in combination with oxaliplatin/5FU (FOLFOX). Tivantinib (ARQ197), a tyrosine kinase inhibitor of c-Met, is also being evaluated with FOLFOX.

Hopefully, we are entering an era in gastroesophageal cancer where treatment decisions will be determined by the patient's and their tumor's molecular characteristics.

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# Personalized Leukemia Care in the Carolinas

**Michael Grunwald,** MD *(left)*
*Medical Oncology*

**Jonathon Gerber,** MD *(right)*
*Medical Oncology*

Levine Cancer Institute is removing obstacles to the care of oncology patients by delivering cancer care closer to home. This summer witnessed the inception of the leukemia program within the Department of Hematologic Oncology and Blood Disorders. The leukemia program provides cutting edge care for patients with acute and chronic leukemias, as well as myelodysplastic syndrome and the myeloproliferative neoplasms. With the planned opening of the blood and marrow transplant (BMT) unit in early 2014 and the introduction of new clinical studies, Levine Cancer Institute will offer optimal and comprehensive care to leukemia patients throughout the Carolinas.

Personalization has increasingly become a goal of leukemia treatment. Indeed, the early recognition that AML is a heterogeneous disease prompted efforts to risk-stratify patients. Current risk assessment is primarily based upon cytogenetic and molecular characteristics. These features help identify poor risk patients who might benefit from consolidation with allogeneic BMT and provide promising targets for both current and future therapies.

Despite this progress, most AML patients who achieve complete remission are not ultimately cured. Existing risk factors are not able to prognosticate well for individual patients, particularly those in the favorable and intermediate risk groups. The leukemia stem cell (LSC) model has gained acceptance as a potential explanation as to why remission often does not translate to cure. Standard chemotherapy is typically effective at wiping out the differentiated bulk of the leukemia, but emerging data suggests that the LSCs are more resistant. The few surviving LSCs may be too few in number to detect by clinically available means. In such cases, the patient appears to be in complete remission. However, any remaining LSCs ultimately regenerate the leukemia, with resultant clinical relapse. As such, only those patients in whom the LSCs are fully eradicated would be predicted to attain cure.

A recently developed flow cytometry-based assay is proving promising in detecting LSCs and predicting which AML patients (who are otherwise in complete remission, based on existing clinical parameters) are likely to relapse.[1] Such assays potentially offer another manner in which leukemia care can be personalized. Patients with persistent LSCs (thus, at high risk of eventual relapse) can be assigned to more intensive therapy such as BMT or to a clinical trial.

Levine Cancer Institute will soon be offering clinical trials with novel targeted agents for hematologic malignancies. We will have the ability - also via a clinical protocol - to assess for the presence of LSCs after treatment. This assay will allow us to determine which novel agents are active against the LSCs and, thus, have curative potential. This ability to personalize therapies and administer them locally whenever feasible will ensure that Levine Cancer Institute delivers the best care possible for patients with leukemia.

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LEARN MORE ABOUT
LEVINE CANCER INSTITUTE AND
OUR CLINICAL TRIALS:
*CarolinasHealthCare.org/updatesincancerV3*

Carolinas HealthCare System
*Levine Cancer Institute*

Carolinas HealthCare System
*Levine Cancer Institute*

UPDATES IN CANCER FOR CLINICIANS

MARCH 2013

# Current Updates in Immunotherapy

Asim Amin, MD, PhD
*Medical Oncology*

Immunotherapy with Interleukin 2 has been the mainstay for treatment of advanced malignant melanoma and renal cell cancer and has shown to induce durable responses in a select population of patients (1, 2). Advances in understanding of immune checkpoints and key cell processes have allowed for development of new immune modulatory approaches (CTLA-4/PD-1 inhibition) and targeted therapy (BRAF/MEK inhibition, VEGF/mTOR inhibition) for both disease processes that are applicable to most of the population.

Generation of anti-tumor immune response by T lymphocytes is a complex process that requires primary antigen presentation in the context of self-HLA molecules by the antigen presenting cells (APCs) constituting signal 1. This is followed by modulation of the immune response by several other interactions between the APC and the T cell – signal 2 (fig. 1) (3). Initially, interaction of an immune-stimulatory molecule CD-28 expressed on the T cell with B7 family of molecules on the APC results in activation of the T cell (fig. 2). Subsequent down-regulation of the T cell activation ensues with expression of an inhibitory molecule CTLA-4 (cytotoxic T lymphocyte antigen 4) on the activated T cell (red) that interacts with the B7 family of molecules on the APC and displaces CD28 (stimulatory signal) leading to inhibition of the T cell. Blocking of the CTLA-4 molecule (the brakes for the immune system) results in uninhibited activity of the T cell that has been shown to translate into clinically relevant anti-tumor activity.

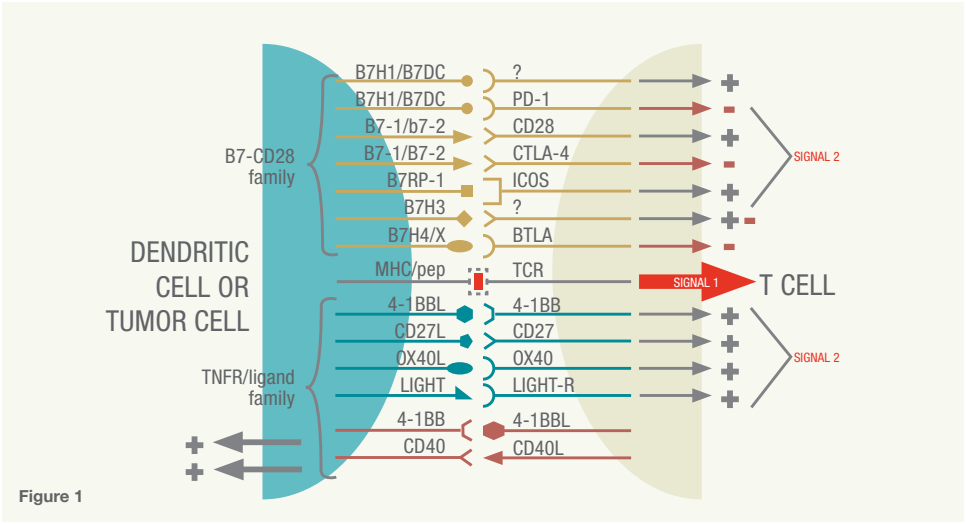



Figure 1

Ipilimumab, an IgG1 antibody directed against the CTLA-4 molecule has shown objective response as well as survival advantage in several phase II, as well as two phase III, trials in patients

CONTINUED ON PAGE 6

# Message from the President of Levine Cancer Institute

Derek Raghavan, MD, PhD
*President*

Dear Colleagues,

I'm pleased to present the second issue of *Updates in Cancer for Clinicians* for your review. Levine Cancer Institute is creating and distributing these publications as a service to our collaborating clinicians. The intent is to provide useful information to keep you abreast of the latest developments in oncology while featuring our new programs offered at Carolinas HealthCare System's Levine Cancer Institute.

In this issue, we have included updates from the recent ASCO GI and GU meetings, featuring new data that may influence your patterns of practice. In addition, we thought that the associated features on neuro-oncology and the emerging roles of immunotherapy might be useful to you.

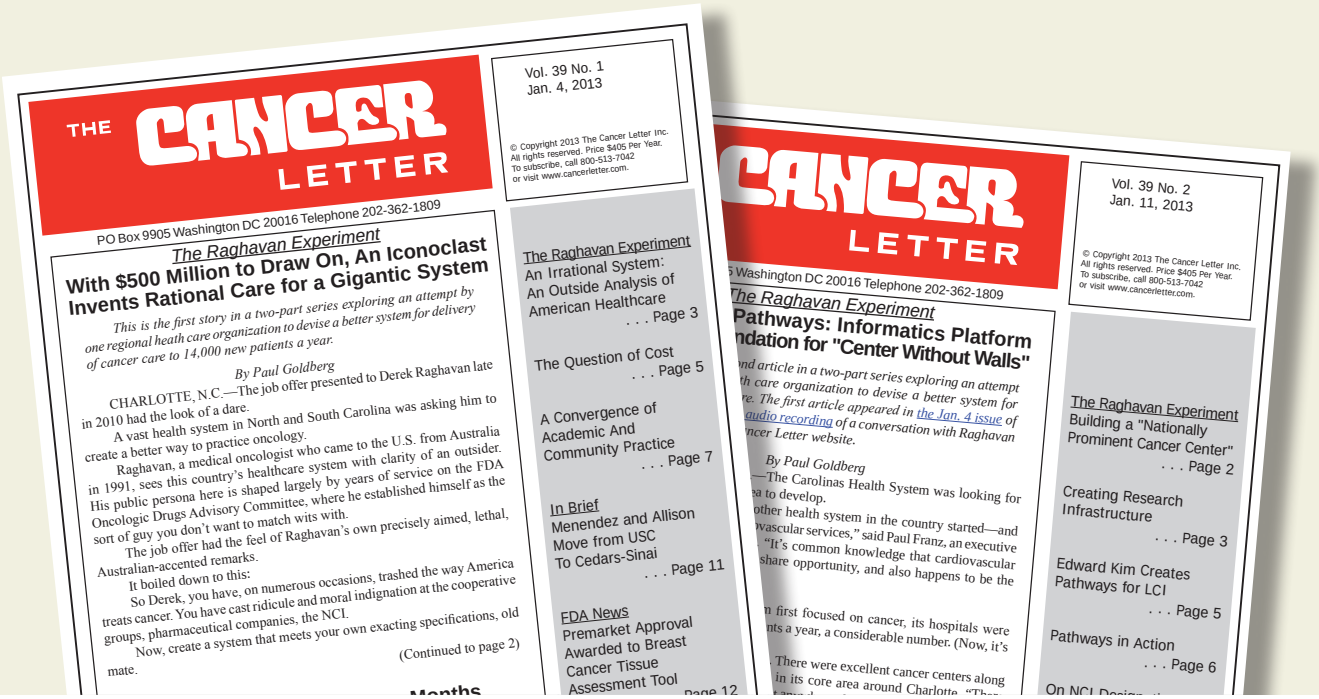
We were very gratified to see the recent coverage of our new research and administrative headquarters along with our academic and clinical programs in two back-to-back issues of *The Cancer Letter*, and I thought you might be interested to read an independent view of our work. Paul Goldberg, a highly respected medical journalist known for his tough coverage of cancer centers, spent a couple of days looking at Levine Cancer Institute, and seems to have been impressed with what he saw!

I hope you find this interesting – please feel free to contact me with any topics you'd like to see covered in future issues. Visit **www.levinecancerinstitute.org/updates-in-cancer** to sign up to receive updates from Levine Cancer Institute or download your free copy of *The Cancer Letter*, with coverage written about the Institute.*

Sincerely,

*We welcome your feedback at* levinecancerinstitute@carolinashealthcare.org *and look forward to bringing you more news in the future!*

## Levine Cancer Institute featured in a two-part series by The Cancer Letter.



THE CANCER LETTER

Vol. 39 No. 1
Jan. 4, 2013

PO Box 9905 Washington DC 20016 Telephone 202-362-1809

The Raghavan Experiment

**With $500 Million to Draw On, An Iconoclast Invents Rational Care for a Gigantic System**

*This is the first story in a two-part series exploring an attempt by one regional heath care organization to devise a better system for delivery of cancer care to 14,000 new patients a year.*

*By Paul Goldberg*

CHARLOTTE, N.C.—The job offer presented to Derek Raghavan late in 2010 had the look of a dare.

A vast health system in North and South Carolina was asking him to create a better way to practice oncology.

Raghavan, a medical oncologist who came to the U.S. from Australia in 1991, sees this country's healthcare system with clarity of an outsider. His public persona here is shaped largely by years of service on the FDA Oncologic Drugs Advisory Committee, where he established himself as the sort of guy you don't want to match wits with.

The job offer had the feel of Raghavan's own precisely aimed, lethal, Australian-accented remarks.

It boiled down to this:

So Derek, you have, on numerous occasions, trashed the way America treats cancer. You have cast ridicule and moral indignation at the cooperative groups, pharmaceutical companies, the NCI.

Now, create a system that meets your own exacting specifications, old mate.

(Continued to page 2)





CANCER LETTER

Vol. 39 No. 2
Jan. 11, 2013

5 Washington DC 20016 Telephone 202-362-1809

The Raghavan Experiment

**Pathways: Informatics Platform ndation for "Center Without Walls"**

nd article in a two-part series exploring an attempt th care organization to devise a better system for re. The first article appeared in the Jan. 4 issue of audio recording of a conversation with Raghavan ncer Letter website.

*By Paul Goldberg*

—The Carolinas Health System was looking for a to develop.

other health system in the country started—and vascular services," said Paul Franz, an executive "It's common knowledge that cardiovascular share opportunity, and also happens to be the

n first focused on cancer, its hospitals were nts a year, a considerable number. (Now, it's

There were excellent cancer centers along in its core area around Charlotte. "Then



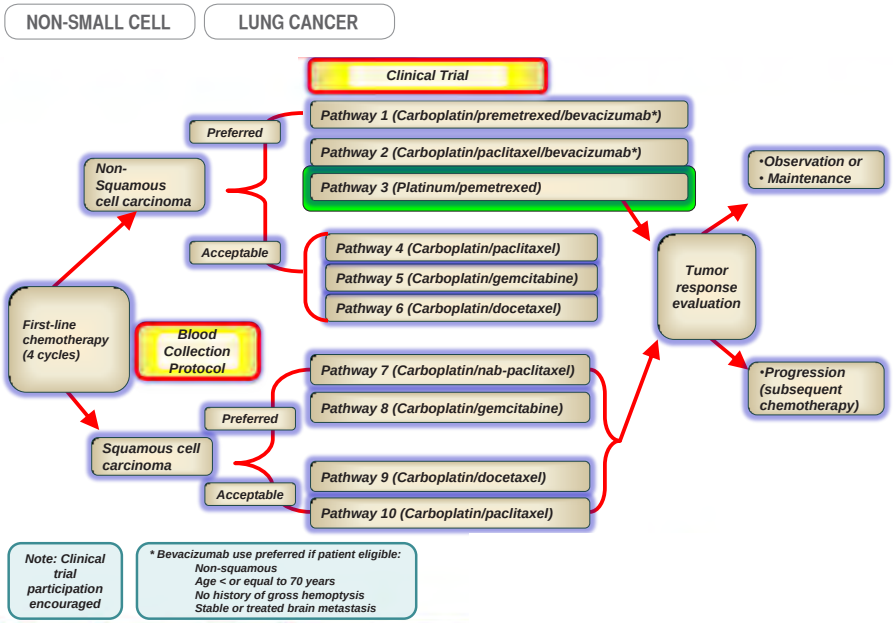


**Permission to distribute has been granted from The Cancer Letter.*

# Creating Clinical Excellence in Patient Care and Biomarker Driven Research

Edward S. Kim, MD *(left)*
*Chair of the Department of Solid Tumor Oncology and Investigational Therapeutics*

Carol Farhangfar, PhD *(right)*
*Assistant Vice President of Tissue Procurement and Research*




The challenge of uniting a system with multiple hospitals and clinics across a large geographic distribution can be daunting. As more options for treatment of cancer patients become approved, the struggle for community medical oncologists becomes more daunting.

We have embarked on several initiatives to create a system that delivers similar clinical care and at the same time, raises awareness for the clinical trial opportunities.

Treatment guidelines were created through working groups utilizing many sources, but most importantly their own practice patterns. Once a consensus was reached, the guidelines were formalized and placed online. The working groups became the tumor sections and meet monthly. Guideline updates are considered each month depending on the amount of new data being reported.

As the pressures mount on seeing more patients and in a timely manner, statistics have shown that national accrual rates to clinical trials have been poor. This has been based on many reasons including limited eligibility, poor variety, time to enrollment, etc.

The clinical pathway tool will be implemented this year for all affiliated clinicians within our Levine Cancer Institute system. This electronic internet-based system will allow practitioners to be informed of the latest treatment pathways. There will also be access to standardized chemotherapy orders, informed consents, drug toxicity forms, chemotherapy teaching sheets, etc. In order to facilitate awareness of clinical trials, this clinical pathway tool will display the open clinical trials in "real-time" fashion.

Our vision at LCI is to create a network that is consistent in clinical care, proactive in accrual to clinical trials, and broad specimen collection for molecular analysis. Both new standard treatment regimens and clinical trials are becoming more integrated with molecular analysis. For example, one of the best known examples is treatment of patients with BRaf V600E mutant melanoma with vemurafenib with new discoveries quickly be added to the molecular testing and targeted treatment repertoire.

We envision adding this type of transformative approach for patient care and translational research at Levine Cancer Institute and Carolinas Healthcare System. Our goal is to support clinical and translational research with a suite of molecular platforms supported by a centralized biospecimen repository. Ultimately, we plan to make molecular testing platforms available where appropriate for all cancer patients. The platforms will include molecular analysis tools such as mutation analysis, copy number, rearrangements, and others needed for our research programs. We will work closely with our colleagues in the Cannon Research Center, Molecular Pathology, our research laboratories and many others to establish best practices. A systematic collection of residual tissue that can be utilized for retrospective studies combined with specific collections to support clinical trials, in particular investigator-initiated studies, will be developed. Clinical annotation of the specimens collected is crucial to support this effort. We plan, as a team, to lead the way integrating advanced genomic and molecular testing into our clinical treatment pathways for cancer patients in the community.

# The Levine Cancer Institute Charter Hospital System: Carolinas Medical Center-NorthEast

Garry Schwartz, MD *(left)*
*Medical Oncology*

Thomas Steffens, MD *(right)*
*Medical Oncology*

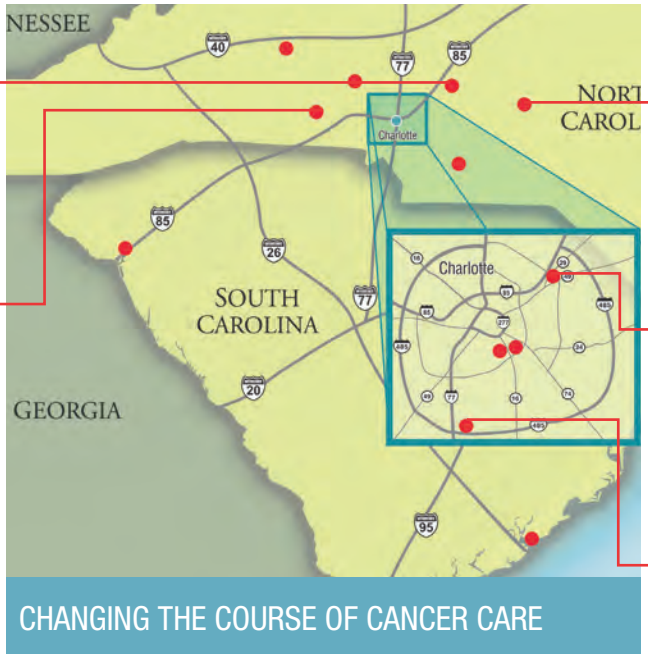
As part of Levine Cancer Institute and Carolinas HealthCare System's charter membership, Carolinas Medical Center-NorthEast, located in Concord, N.C., provides patients in Cabarrus, Rowan and surrounding counties in North Carolina greater access to world-renowned cancer specialists, treatment options and clinical trials when and where they're needed most. Levine Cancer Institute is changing the course of cancer care by removing the barriers that separate patients from world-class research, breakthrough treatments and quality cancer care.

Work is well under way to develop even more survivorship and outreach programs in the counties surrounding CMC-NorthEast. Levine Cancer Institute offers a full spectrum of services to support patients before, during and after treatment, to improve long-term care and patients' quality of life. The Institute and CMC-NorthEast are piloting programs to understand the accessibility issues cancer patients in rural areas face and addressing those issues through transportation, home healthcare, community education and other means. And because of the breadth and depth of Carolinas HealthCare System, the Institute is also able to conduct more research and collaborate with more cancer specialists. Drs. Steffens and Schwartz represent oncology specialists who collaborate closely with the Institute participating in pathway development and clinical research.

The relationship between Levine Cancer Institute, CMC-NorthEast and the other member institutions located throughout the Carolinas brings increased access to cancer specialists, research and innovative programs and services to patients closer to where they live.

CMC-NorthEast

CMC-Lincoln




CHANGING THE COURSE OF CANCER CARE

Stanly Regional Medical Center

CMC-University

CMC-Union

# Advances in Gliobastoma
# Updates from Society of Neuro-Oncology 2013


Ashley Sumrall, MD *(left)*
*Neuro-Oncology, Medical Oncology*

Dan Haggstrom, MD *(right)*
*Medical Oncology*


Stuart Burri, MD *(left)*
*Radiation Oncology*

Anthony Crimaldi, MD *(right)*
*Radiation Oncology*


Anthony Asher, MD, FAANS, FACS *(left)*
*Neurological Surgery*

Morgan Stuart, MD *(right)*
*Neurological Surgery*

Should bevacizumab be given in newly diagnosed glioblastoma? Can we improve the median overall survival as reported by Stupp to be 14.6 months? Opinions differ and much has been offered anecdotally on the topic. Evidence has been sparse on the topic, and no randomized trials have been completed. Safety of administering bevacizumab in the newly diagnosed setting was deemed acceptable based on data from several small pilot studies.

A nonrandomized, phase II study from Duke followed 75 patients with newly-diagnosed glioblastoma who received concurrent chemoradiotherapy and bevacizumab. Median overall survival (as measured from time of enrollment) was 21.2 months and median progression-free survival topped 14 months (95 percent CI: 12-16). Another nonrandomized study from UCLA followed 70 patients with glioblastoma. They received similar therapy with bevacizumab. Median overall survival (as measured from date of diagnosis) was 19.6 months and median progression-free survival was just shy of 14 months (95 percent CI: 11-16). These data appear similar, but the different definitions of survival are significant. Attempts to solve the dilemma have been initiated by RTOG (RTOG 0825) and Roche (AVAglio).

AVAglio is a large, randomized, double-blind, placebo-controlled, phase III trial evaluating the addition of bevacizumab to the current standard of care for newly diagnosed glioblastoma. Patients had acceptable KPS scores and were all ages. Approximately 90 percent of the sample consisted of patients who had maximal tumor resection. In total, more than 900 patients were enrolled at more than 140 centers worldwide. At the recent Society of Neuro-Oncology Annual Meeting in Washington, DC, preliminary results from AVAglio were released to much anticipation. Investigators reported a 36 percent risk reduction in progression of disease or death. Median PFS of 10.6 months from time of enrollment was observed (compared to 6.2 months in the control arm). Investigators reported significant improvements in standardized quality-of-life assessments between the arms. Also, average steroid requirements were lower in the experimental arm. There is no doubt that the overall survival data from this study will be anxiously awaited. The RTOG 0825 data will hopefully mature soon, and will likely enrich this ongoing discussion.

# Current Updates in Immunotherapy

CONTINUED FROM PAGE 1

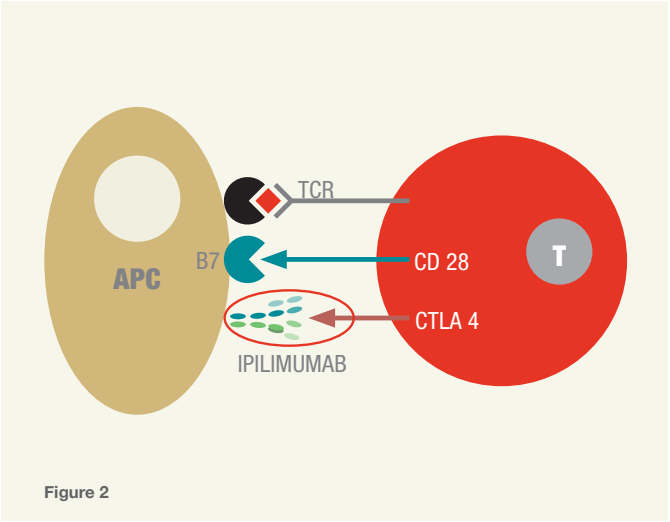



Figure 2

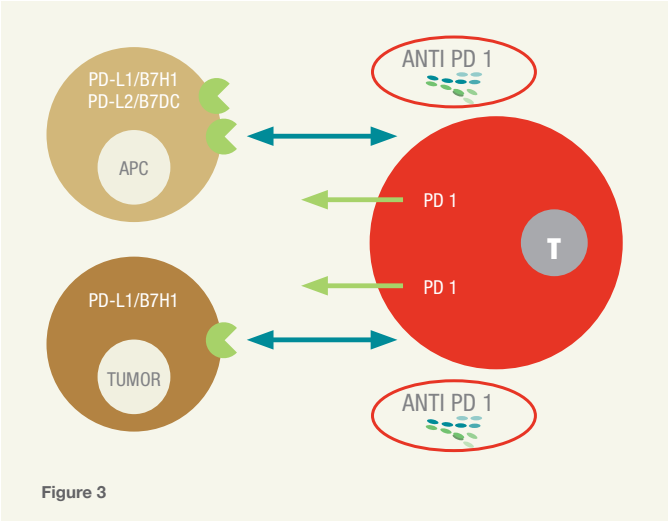



Figure 3

with advanced melanoma (4, 5). The treatment is generally tolerated well, but may result in toxicity peculiar to the mechanism of action (uninhibited T cell activation) in the form of auto-immune breakthrough events (dermititis, colitis, endocrinopathy, hepatitis) that if not recognized and managed appropriately can result in significant morbidity and even death.

Identification of mutant BRAF (a component of the MAP kinase signaling pathway) in almost 50 percent of cutaneous melanomas has led to the development and approval of vemurafinib, a BRAF inhibitor (BRAFi) having shown survival advantage in a phase III study (6). Responses observed with BRAFi are rapid and substantial however generally not durable.

We are currently in the process of studying the combination of BRAFi followed by immune modulation with CTLA-4 inhibition and the role of vertical blockade with BRAF and MEK inhibition. PD-1 (programmed cell death protein 1) is yet another inhibitory checkpoint expressed on the surface of T cells that can interact with its ligands PDL-1 and PDL-2. Interaction with either results in suppression of the T cell (fig. 3). Interestingly, PDL-1 may be expressed not only on APCs but some tumor cells thereby providing a potential protective mechanism directly to the tumors against immune anti-tumor mechanisms. Blocking of the PD-1 molecule with an anti-PD-1 antibody results in preventing the T cell to be switched off and thereby exert anti-tumor effect. In the phase I setting PD-1 inhibition has exhibited responses in the range of (20-30 percent) in various tumor types including, melanoma, renal cell carcinoma and non-small cell lung cancer (7).

We are currently studying the combination of VEGF tyrosine kinase inhibition in combination with anti-PD-1 therapy for patients with advanced renal cell carcinoma and the role of anti-PD-1 monotherapy for patients with advanced melanoma whose disease has progressed after treatment with CTLA-4 inhibition.

In the context of immunotherapy, yet another approach has been to harness the activity of APCs for more effective presentation of tumor antigen to the T cells. A study using autologous tumor mRNA from the kidney tumor harvested at the time of nephrectomy for priming of autologous APCs in combination with sunitinib showed improvement in overall survival for intermediate and poor risk patients compared to historical controls treated with sunitinib alone (8). We are now embarking on a phase III study to confirm addition of immunotherapy adds durability to responses observed with VEGF inhibition alone.

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# Expanding Options for Patients with Metastatic Castrate Resistant Prostate Cancer


Earle Burgess, MD *(left)*
*Medical Oncology*

Steve Riggs, MD *(right)*
*Urologic Oncology*


John Mahoney, MD *(left)*
*Medical Oncology*

Kris Gaston, MD *(right)*
*Urologic Oncology*

Improved understanding and pharmacologic targeting of the androgen pathway has recently benefited patients with advanced prostate cancer following regulatory approval of abiraterone and enzalutamide in this population. Abiraterone acetate, a potent inhibitor of CYP17, impairs adrenal androgen synthesis leading to greater reduction of systemic testosterone levels than achieved with medical or surgical castration alone. The importance of targeting extragonadal androgen synthesis was underscored by the results of the COU-AA-301 trial(1). In this randomized phase III trial, patients with metastatic, castrate resistant prostate cancer, previously treated with docetaxel, received either abiraterone or placebo with prednisone. The trial was unblinded following preplanned interim analysis showing a 3.9 month overall survival benefit in the abiraterone arm, providing the basis for FDA approval of abiraterone after chemotherapy. Often patients with castrate resistant disease are not ideal candidates for docetaxel-based therapy due to age or medical comorbidities; therefore, the findings of the companion COU-AA-302 trial are of particular interest to practioners (2). In this study, men with chemonaive metastatic, castrate-resistant prostate cancer also received either abiraterone or placebo with prednisone. With a median follow up duration of 22.2 months, abiraterone plus prednisone reduced the risk of death or radiographic progression by 47 percent compared to the placebo arm (8.3 vs. 16.5 months, p <0.001). These results led to an expanded FDA approved indication to include men previously untreated with docetaxel, providing an effective new treatment option for patients prior to or in lieu of chemotherapy.

Enzalutamide, a high affinity androgen receptor antagonist, has also recently demonstrated an impressive 4.8 month overall survival benefit in men with advanced, castrate-resistant prostate cancer after prior docetaxel (3). Like abiraterone, enzalutamide is anticipated to demonstrate activity in the pre-chemotherapy setting, though until results of the PREVAIL trial (NCT01212991) are available, routine use should be reserved for patients previously treated with docetaxel. Although the activity of these new agents highlights the critical role androgen signaling continues to play in driving prostate cancer progression following castration, pharmacologic targeting of other molecular pathways is also showing promise. c-MET is an oncogenic receptor tyrosine kinase that is inhibited by the small molecular cabozantinib. A randomized phase II trial of cabozantinib in men with advanced prostate cancer was halted early on the basis of significant radiographic and clinical benefit observed in the cabozantinib arm (4). The results of ongoing phase III trials of cabozantinib in advanced prostate cancer are eagerly anticipated.

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# Updates from GI ASCO 2013


Jean Chai, MD *(left)*
*Medical Oncology*

Reza Nazemzadeh, MD *(right)*
*Medical Oncology*


Stuart Salmon, MD *(left)*
*Medical Oncology*

Josh Hill, MD *(right)*
*Surgical Oncology*

While many investigators have spent years looking at combination chemotherapy in the hopes of improved survival for metastatic pancreatic cancer, the results have been disappointing. In fact, single agent gemcitabine is still recognized as a standard treatment option, especially in the patients who have poorer performance status. A promising recent advance has been an aggressive combination of fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) showing a 3.6 month survival advantage and a response rate of more than 30 percent. However, this has proven to be a difficult regimen in clinical practice.

At the 2013 GI ASCO, Daniel von Hoff and colleagues presented the results of MPACT, a large randomized trial evaluating the combination of nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas. The experimental arm gave Nab-paclitaxel at 125 mg per meter squared and gemcitabine at 1000 mg per meter squared on days 1, 8 and 15 every 28 days. The control arm used gemcitabine dosed at 1000 mg per meter squared weekly for 7 weeks then on days 1, 8, and 15, every 4 weeks. 861 patients received treatment between the two arms. The experimental arm had an overall survival of 8.5 months compared to 6.7 months with single agent gemcitabine. While this improvement was modest, the one-year survival was 35 percent in the experimental arm which was significantly greater than the control arm at 22 percent. There was a two-year survival rate of 9 percent in the experimental arm, but only 4 percent with single agent gemcitabine. Response rates are also increased at 22 percent with nab-paclitaxel plus gemcitabine versus 7 percent with gemcitabine alone

Nab-paclitaxel plus gemcitabine appears to be an active and more tolerable alternative for metastatic pancreas cancer. Reflecting the typical patient population in community practice, a large number of patients with a Karnofsky performance status of 70 percent or greater (ECOG 0-2) were included and 42 percent of patients were 65 years or older. In contrast, the trial investigating FOLFIRINOX was comprised of a younger cohort with better performance status, and yet there appeared to be greater toxicity.

Another intriguing study was the SCALOP trial, which studied the approach of induction chemotherapy with gemcitabine plus capecitabine, followed by concomitant radiation with either gemcitabine or capecitabine. The combination of gemcitabine plus radiation was associated with increased fatigue and hematologic toxicity, while achieving inferior 9-month progression free survival (gemcitabine 51.4 percent vs capecitabine 62.9 percent) and overall survival (gemcitabine 13.4 months vs capecitabine 15.2 months).

In gastric and GEJ cancers, two interesting studies were presented. The COUGAR-02 trial confirmed a survival benefit with second line chemotherapy compared to best supportive care in a very nice randomized trial from the UK. This trial studied second line docetaxel in patients with gastric, esophageal, and GEJ cancer. Overall survival with docetaxel was 5.2 months vs 3.6 months with active supportive care, thus validating the utility of chemotherapy in these patients

A novel targeted agent, Ramucirumab, a fully human IgG1 monoclonal antibody targeting VEGF-receptor 2, was found to be active in gastric and GEJ cancer. Ramucirumab increased overall survival in the second line setting compared to placebo in a randomized, double-blind, placebo controlled phase III trial. Patients treated with ramucirumab had a median OS of 5.2 months vs 3.8 months for placebo. Disease control rate was 49 percent for ramucirumab compared to 23 percent. This will certainly lead to further study of Ramucirumab in other settings and in combination with chemotherapy.

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# UPDATES IN CANCER FOR CLINICIANS

JANUARY 2013

## Updates from ASH 2012:

### *Gene Encoding and Sequencing to Personalize Therapy*

Edward Copelan, MD *(right)*
*Chair of the Department of Hematologic Oncology and Blood Disorders*

Belinda Avalos, MD *(left)*
*Vice Chair of the Department of Hematologic Oncology and Blood Disorders*

Two important themes of the 2012 ASH meeting emerged from special lectures given by Carl June, MD, from the University of Pennsylvania and recipient of the Ernest Beutler Award, and Tim Ley, MD, from Washington University and E. Donnall Thomas Award recipient. Dr. June presented striking results using tumor-specific cellular immunotherapy in two lymphoid malignancies, CLL and ALL. June and colleagues introduced genes encoding artificial receptors called chimeric antigen receptors (CARs) into patients' autologous T cells in vitro in order to redirect the specificity of these immune effector cells to the B cell-specific CD19 antigen. CAR proteins expressed on T cells were composed of an antibody that could bind to a specific target (here the CD19 antigen found on B cell leukemias) fused to a transmembrane domain followed by one or more cytoplasmic signaling domains to generate proliferative and antitumor activity. A T cell engineered with this design could specifically recognize a leukemia cell, kill it, disengage and kill another—then divide and make more engineered T cells so that one cell could kill more than 1,000 leukemia cells following injection, meriting it the moniker "serial killer." In addition to achieving sustained complete remissions in four of nine evaluable patients with refractory CLL, complete remission was also obtained in a child with ALL who experienced life-threatening cytokine storm associated with tumor lysis that was successfully treated with TNF and IL-6 antagonists. Along with accrual of larger numbers of patients with B-Cell malignancies, new protocols are currently being developed to extend the groundbreaking work of cancer-specific T cells to pancreatic, prostate and breast cancer.

Dr. Ley summarized his own work and that of others, including several presentations at the meeting, using whole genome sequencing to study clonal evolution in large numbers of patients with AML. By sequencing several hundred primary tumor and relapse genomes, Ley and colleagues have provided an unprecedented view of the development and evolution of AML. A series of non-transforming mutations appear to accumulate with age in pre-leukemic stem cells. A dominant mutation cluster consisting of genes recurrently mutated in AML leads to leukemic transformation by a founding clone. Extensive mutational analysis can be used to discriminate intermediate risk AML patients into clinically relevant groups with distinct prognoses and to delineate patients who would and would not benefit from intensified chemotherapy and/or transplantation. Relapse of AML results either from a founding clone which gains mutations that confer a survival advantage or from a subclone of the founding clone, detectable at diagnosis, which survives initial therapy, gains new mutations and expands at

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# Message from the President of Levine Cancer Institute

Derek Raghavan, MD, PhD, *President*

Carolinas HealthCare System's Levine Cancer Institute is built on the concept of cancer care without walls, spanning throughout the system's network of affiliated hospitals and providers in the Carolinas. The Institute is working to define the future of cancer care – where innovations in research, clinical trials, patient support and treatment are brought closer to home for patients.

We continue to build an elite cancer program, with the recruitment of internationally renowned experts to lead the clinical teams. From the University of Texas MD Anderson Comprehensive Cancer Center, Edward S. Kim, MD, will serve as chair of the Department of Solid Tumor Oncology. Edward A. Copelan, MD, FACP, from Cleveland Clinic's Taussig Cancer Institute will serve as chair of the Department of Hematologic Oncology and Blood Disorders. We have recruited more than 50 faculty from the Carolinas and across the USA.

Updates in Cancer for Clinicians will inform you on exiting news from Levine Cancer Institute.

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*We welcome your feedback at* levinecancerinstitute@carolinashealthcare.org *and look forward to bringing you more news in the future!*

Levine Cancer Institute Research and Administrative Headquarters.

A view of the infusion floor at Levine Cancer Institute.

# Translational Science

## *Pharmacogenic Approaches to Personalize Cancer Therapy*

Ram Ganapathi, PhD *(left)*
*Chair of Cancer Pharmacology*

Marukh Ganapathi, PhD *(right)*
*Senior Scientist*

Complexities in the genetic landscape of tumors significantly impact the design of optimal strategies for effective treatment of cancer. The goal of Cancer Pharmacology/Translational Research at Levine Cancer Institute is to support and develop novel paradigms for cancer care. As such, our ongoing translational research has focused on the areas of acute myeloid leukemia (AML), renal cell carcinoma and ovarian cancer.

A key event in the development of AML is the disruption of the myeloid differentiation program and aberrant self-renewal of leukemic stem cell. Differentiation therapy with the retinoic acid analog, all-trans retinoic acid (ATRA) has been successful in treating acute promyelocytic leukemia, a cytogenetically distinct subtype of AML characterized by the PML-RARα gene translocation. However, ATRA has shown little promise in differentiation therapy of other subtypes of AML. To develop strategies that would improve differentiation therapy for other forms of AML, including relapsed/refractory disease, we studied the role of a key nuclear enzyme, topoisomerase II, in ATRA-induced differentiation of AML cells. Using different AML cell lines and AML blast cells from relapsed/refractory patients, we were able to demonstrate that by targeting topoisomerase II, either by deleting the enzyme or inhibiting its activity, the therapeutic efficacy of ATRA could be potentiated. Specifically, the combination of ATRA and topoisomerase II inhibitors, such as ICRF-193 or dexrazoxane (a clinically active topoisomerase II inhibitor), led to enhanced differentiation and preferential activation of the cell death pathway, as compared to differentiation coupled growth arrest induced by ATRA alone. Based on this preclinical finding, we were able to formulate a clinical hypothesis that the combination of ATRA with the clinically relevant topoisomerase II catalytic inhibitor, dexrazoxane, leads to improved response in AML patients. We are now poised to test this hypothesis in

CONTINUED ON PAGE 7

# Novel Treatments for Lung Cancer Patients With EGFR Mutations

Edward S. Kim, MD *(left)*
*Chair of the Department of Solid Tumor Oncology and Investigational Therapeutics*

Kathryn Mileham, MD *(right)*
*Medical Oncology*

Lung cancer remains the leading cause of cancer-related deaths in the United States, (1) and non-small cell lung cancer (NSCLC) accounts for more than 85 percent of the cases. With most patients presenting with advanced disease, there is an urgency to maximize treatment efficacy while minimizing drug toxicity. Through a deeper understanding of the biology driving NSCLC, novel treatment paradigms are based on disease biomarkers with corresponding targeted therapy. This has been best achieved with advanced treatment options for the two-thirds of adenocarcinoma patients in whom driver mutations are identified.

Somatic mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) are found in 15-20 percent of lung adenocarcinomas.

Afatinib is an oral small-molecule EGFR-tyrosine kinase inhibitor that binds irreversibly to EGFR and HER2. Recent compelling data from the LUX-Lung 3 trial have been reported. In this randomized phase III study, patients with EGFR-mutated, advanced lung adenocarcinomas were treated frontline with afatinib versus pemetrexed-cisplatin. The study enrolled 345 patients and met its primary endpoint demonstrating significantly prolonged progression free survival (PFS) in patients treated with afatinib (11.1 vs 6.9 months; HR, 0.58; p=0.0004). In preplanned analysis, those patients with common mutations (Del19 or L858R) had a median PFS of 13.6 versus 6.9 months (HR, 0.47; p<0.0001). (2) Additionally, objective response rate, disease control, cancer-related symptoms and quality of life were also improved with afatinib. The most frequent adverse events were diarrhea and rash, although no patients discontinued afatinib for rash. LUX-Lung 3 is the first randomized study to demonstrate benefit of an oral targeted therapy versus chemotherapy in a molecularly selected population. Based on these results, afatinib is currently available through an open label expanded access program at a starting dose of 40 mg/daily.

While management of lung cancer is in rapid evolution the standard of "chemotherapy for all" no longer exists. National guidelines concur that molecular profiling is necessary in order to provide the best available therapy. This requires sufficient tissue sampling for precise pathologic diagnosis. While patients with unknown driver mutations are still treated with chemotherapy, those with EGFR mutations or ALK rearrangements have expanding options for targeted personalized treatment.

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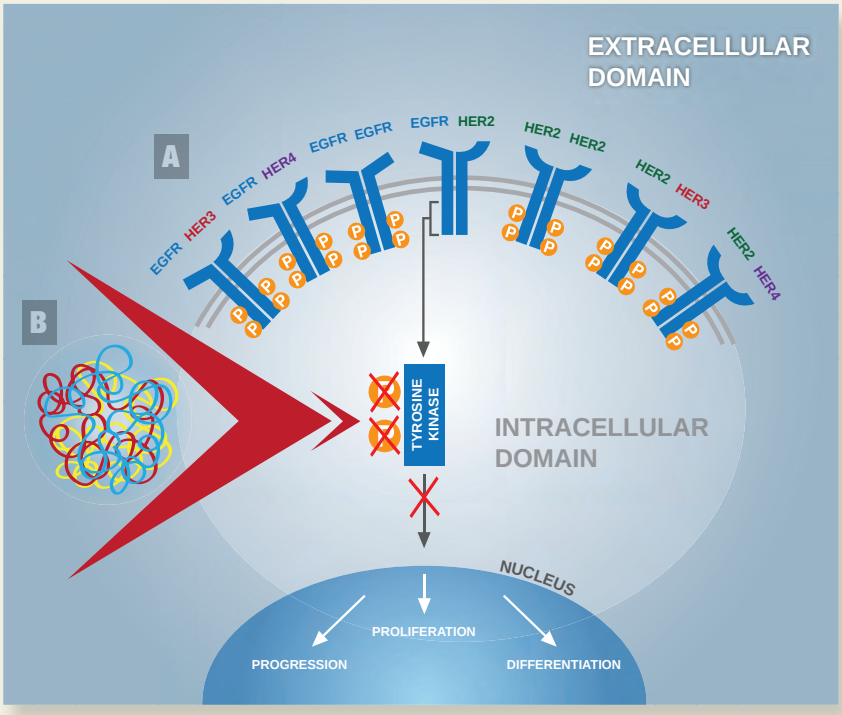


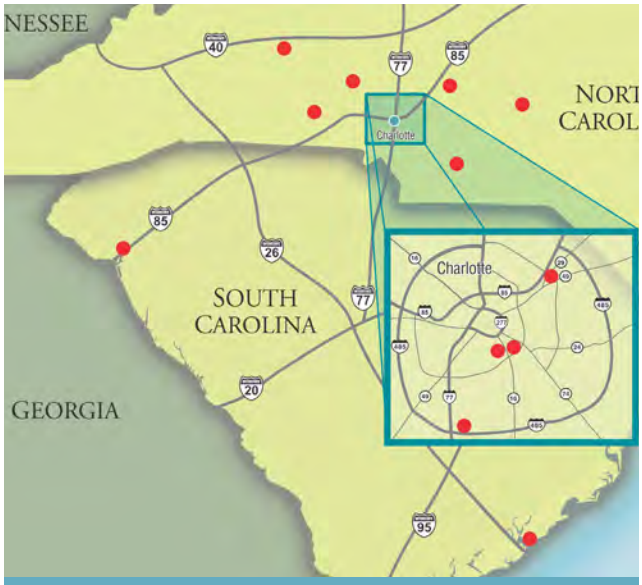

**A:** The epidermal growth factor family of extracellular protein ligands includes cell surface receptors EGFR (ErB-1), HER2 (ErB-2), HER3 (ErB-3), and HER4 (ErB-4). When EGFR is dimerized, intrinisic intracellular tyrosine kinase activity is stimulated by autophosphorylation causing downstream activation and signaling leading to DNA synthesis and cell proliferation.

Mutations in EGFR are clustered near the tyrosine kinase domain possibly providing stabilization and additive gain. Therapeutic approaches targeting EGFR tyrosin kinase halt this signaling cascade.

**B:** Afatnib is an oral, small-molecule, EGFR-tyrosine kinase inhibitor that irreversibly binds to the ErbB family homo- and heterodimers inhibiting signal transduction.

# Levine Cancer Institute: Built on the Strength of a Network

At Levine Cancer Institute we've developed a sophisticated academic and clinical cancer institute without walls, spanning Carolinas HealthCare System (CHS) and providing state-of-the-art treatment and research programs are closer to where our patients live.




CHANGING THE COURSE OF CANCER CARE

The Institute's research and administrative headquarters located in Charlotte, NC, opened in October 2012. While the Institute functions as a series of integrated cancer programs distributing high-quality cancer care system-wide, this building serves as its center for communication, research and administration. It houses the technology infrastructure to seamlessly connect physicians and care teams and share best practices and programs.

The building features nine cancer clinics, infusion therapy, palliative care, as well as cutting-edge teleconferencing technology that allows physicians to collaborate long-distance, further breaking down geographic barriers and improving care across CHS. With six floors and more than 171,000 square feet of space, the building includes an extensive clinical trials operation with a special Phase I therapeutic unit designed to evaluate new treatment options, and multidisciplinary clinics to treat complex and rare cancers.

"The opening of the building is symbolic of the entire Levine Cancer Institute network being fully functioning, for the advancement of patient care across the Carolinas," said Dr. Derek Raghavan. "The new resources and technology this space affords will enable us to be better connected to our partner institutions across the Carolinas to share knowledge, standard protocols and research, while offering patients in Charlotte a state-of-the-art place to receive their cancer care."

# Integration of Roper St. Francis Cancer Care Into Our Network

Steve Akman, MD,
*Medical Director, Roper St. Francis Cancer Care*

In 2012, Carolinas HealthCare System's Levine Cancer Institute announced its charter member institutions, including Roper St. Francis Cancer Care, as part of the system's new cancer care network.

Roper St. Francis Cancer Center was established in 2010 through a partnership between Roper St. Francis Healthcare and Charleston Hematology Oncology Associates. The 76,000 square-foot outpatient cancer center is home base for many of the services provided by Roper St. Francis Cancer Care physicians, who help more than 1,700 newly diagnosed cancer patients each year. Top tumor sites include breast, prostate, lung and colorectal cancers. Roper St. Francis Cancer Care is the market leader by volume for breast, prostate and colorectal cancers*.

The relationship between Levine Cancer Institute, Roper St. Francis Cancer Care and other member institutions brings increased access to cancer specialists, research and innovative programs and services to patients closer to where they live.

"We take cancer care very seriously. Through our elite network of affiliated hospitals and physicians across the Carolinas, we are able to bring patients the best cancer care in a more convenient way," said Derek Raghavan, MD, PhD, and President of the Institute. "Levine Cancer Institute is a national model that shows how we are investing in our community and the lives of patients by removing barriers that separate them from access to breakthrough research and treatments."

" The providers and patients of Roper St. Francis Healthcare are excited about our partnership with Levine Cancer Institute," said Steven Akman MD, Medical Director of Roper St. Francis Cancer Care. "This partnership facilitates rapid access to advanced cancer therapies and technologies in our Charleston community that heretofore had only been available to institutions of the size and scale of Levine Cancer Institute."

**Based upon 2010 data provided by the Commission on Cancer of the American College of Surgeons*

# Highlights from SABC 2012


Wendy Brick, MD *(left)*
*Medical Oncology*

Richard White, MD, FACS *(right)*
*Surgical Oncology*


Steven Limentani, MD *(left)*
*Medical Oncology*

Teresa Flippo-Morton, MD, FAC *(right)*
*Surgical Oncology*

## The ATLAS Trial: Treatment Implications

While current treatment guidelines recommend that women with estrogen receptor positive breast cancer receive anti-estrogen therapy for five years, the recently published results of the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) results suggest that 10 years of adjuvant treatment should be considered for some women.

The international trial recruited patients from 1996-2005 and enrolled patients were randomized to stop tamoxifen at five years (control) or continue for a total of 10 years. Allocation to continue tamoxifen for 10 years versus stopping at five years reduced breast cancer recurrence (617 recurrences in 3,428 women allocated to continue versus 711 in 3,418 controls p=0.002) and breast cancer mortality (311 deaths with recurrence in women allocated to continue versus 397 in controls p=0.01). Risk of recurrence during years 5-14 was 21.4 percent for continuing tamoxifen versus 25.1 percent for controls (absolute risk reduction 3.7 percent). Breast cancer mortality during these same years was 12.2 percent versus 15 percent, for an absolute mortality reduction of 2.8 percent. The greatest additional benefit was seen in the second decade after diagnosis, as there was almost no difference in death and recurrence between the two groups during the five years of extra tamoxifen. The difference came in later years, consistent with the understanding that tamoxifen has an effect that lasts long after women stop taking it. Breast cancer mortality during the second decade after diagnosis was decreased almost 30 percent in women who continued tamoxifen for 10 years.

These results are relevant for any woman currently taking tamoxifen and may be even more so for premenopausal women, who have little risk of tamoxifen causing uterine cancer or venous thrombotic events. Women and their doctors should consider this evidence when deciding how long to continue tamoxifen or any other endocrine therapy.

Evaluation of the long-term side effects of longer term tamoxifen will require lengthier follow up and meta-analysis of all relevant trials for final assessment.

REFERENCE:
*The Lancet, 2012 DOI: 10.1016/S0140-6736(12)61963-1*

## Racial and Staging Disparities

Racial disparities in the care of women with breast cancer have become the norm rather than the exception (MMWR 2012, Lund 2008, van Ravesteyn 2011). Investigators from MD Anderson Cancer Center used SEER Medicare data to assess the utilization of the relatively new technology of axillary sentinel lymph node biopsy (SLNB) in the staging of women with breast cancer. The use of SLNB was compared in white women versus the use in black women.

5.7 percent of 31,274 women retrieved from the database were black while 89 percent were white. 74 percent of the white women underwent SLNB, compared to 62 percent of the black women (p<0.001). Further analysis noted differences between 7 and 15 percent for every year from 2002 to 2007. With adjusted analysis, black women were 33 percent less likely to undergo SLNB than white women (relative risk=0.74, 95 percent CI 0.67-0.81, p<0.001).

Black women in the U.S. have a 41 percent higher breast cancer death rate than white women despite a lower incidence. 45 percent of black women are diagnosed with regional or distant disease versus 35 percent of white women [MMWR 2012]. Van Ravesteyn [2011] proposed a model suggesting that differences in screening use explained 8 percent and differences in adjuvant therapy explained 19 percent of these disparities. Methods to address disparities are being tested throughout the U.S. and are critical to changing the course of cancer care.

REFERENCE:
Black DM, San Antonio abstract 2012

## Axillary Node Dissection May Not Be Needed For Everyone

ACOSOG Z-1071 studied the use of sentinel node biopsy in a group of women with breast cancer who had previously been considered contraindicated for this procedure; biopsy-proven node positive women. This multicenter trial enrolled 756 women with node positive breast cancer.

All patients received neoadjuvant chemotherapy prior to surgery. All women had re-evaluation of the axilla with ultrasound and then surgery with a sentinel lymph node procedure (encouraging both blue dye and radionucleotide for mapping), followed by complete axillary node dissection.

CONTINUED ON PAGE 6

# Highlights from SABC 2012

CONTINUED FROM PAGE 5

Results demonstrated that 40 percent of patients with positive sentinel lymph node prechemotherapy had a complete pathologic response in the axilla. The false negative rate of the procedure was 12.6 percent, though the SLN procedure was able to correctly identify nodal status in 91 percent of patients. Further evaluation of the data is needed before this can routinely change practice, but it does give hope that a subset of women with node positive disease in the axilla may, in the future, be able to omit an automatic axillary node dissection.

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*2. Johnson K, " In Node-Positive Breast Cancer, Sentinel Biopsy Could Avert ALND", Medscape, Dec 6, 2012.*

## TDM-1, Docetaxel and Pertuzumab in Breast Cancer Patients

T-DM1 is a drug in which Trastuzumab has been covalently linked to a novel chemotherapeutic emtansine, also known as DM1. Pertuzumab, in contrast, interferes with her2- her3 dimerization, a novel action different from the mechanism action of Trastuzumab.

This phase I dose escalation study was performed beginning with stage IV disease patients, but also those with stage II and stage III breast cancer treated in the neoadjuvant setting followed by an expansion cohort. Sites for this study included Levine Cancer Institute, Baylor College of Medicine and multiple sites in Europe.

The study demonstrated that doublet and triplet combinations were well tolerated. Early analysis of patients treated in the neoadjuvant setting revealed eight of nine (88 percent) treated with the doublet and three of five (60 percent) treated with the triplet regimen achieved a pathologic complete response in the breast and lymph nodes. More data will be available once all patients have undergone the surgical portion of their treatment. Although the numbers are small, the rate of pathologic complete response is encouraging. Data will be utilized as the basis for a phase III randomized trial that will compare these combinations to the current standard of care for women with breast cancer treated in the neoadjuvant setting.

REFERENCE:
*Martin Miguel; "Interim Results From a Phase 1b/2a Study of Trastuzumab Emtansine and Docetaxel, With and Without Pertuzumab, in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer", presented at San Antonio Breast Cancer Symposium, Dec. 5, 2012, San Antonio, Texas.*

## Updates from ASH 2012: *Gene Encoding and Sequencing to Personalize Therapy*

CONTINUED FROM FRONT PAGE

relapse. A comparison of relapse versus primary tumor mutations demonstrated increased numbers of transversions at relapse, likely resulting from cytotoxic chemotherapy.

In addition, Francesco Lo-Coco, MD, from the University of Rome Tor Vergata, presented interesting results from a phase III, randomized, prospective trial from the Italian GIMEMA group and German SAL and AMLSG groups at the Plenary Session. Data demonstrated a two-year, non-inferior EFS in adult patients with newly diagnosed non-high-risk APL (WBC ≤10x109/L) treated with a chemotherapy-free regimen of ATRA and arsenic trioxide compared to standard ATRA + Idarubicin.

Together, these presentations demonstrate that the leukemic genome in an individual patient is a "moving target", whose cure requires eradication of the founding clone and its subclones, but offers clinicians better tools for risk assessment and selection of existing initial therapy and new weapons, including "serial killer" cells, for the melee.

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*3. Fisher A, Daniel C, et. all; 54th American Society of Hematology Annual Meeting, Atlanta, GA, 2012 Abstract 706.*
*4. Porter David L, et. all; 54th American Society of Hematology Annual Meeting, Atlanta, GA, 2012 Abstract 717.*
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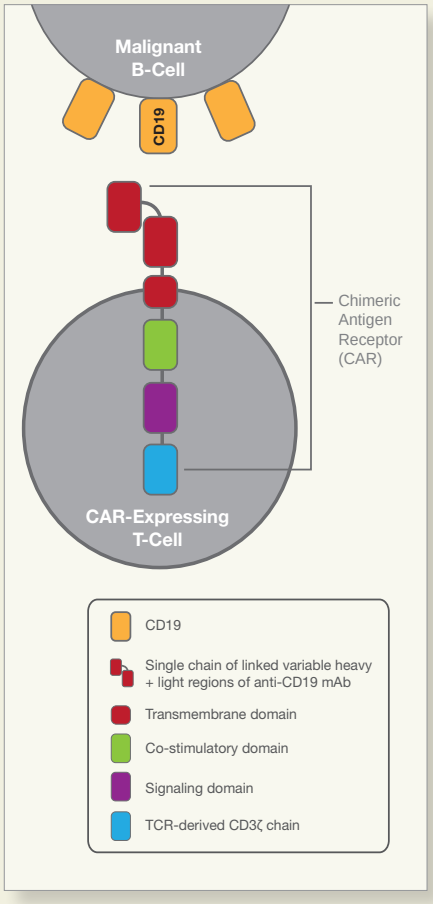


**Figure 1:** Genetically Engineered Adoptive Cell Therapy Via Car-Expressing T-Cells.

# Translational Science

## *Pharmacogenic Approaches to Personalize Cancer Therapy*

CONTINUED FROM PAGE 5

preclinical mouse models that mimic relapsed/refractory AML. This study will serve as a platform in the development of a clinical protocol for treating AML.

In the past few years, treatment of renal cell cancer has included the discovery and approval of drugs that target angiogenesis related pathways. However, the rapid entry of these drugs in clinical practice has not kept pace with our understanding of treatment associated toxicity and mechanisms governing response to optimize therapy. We have embarked on a pharmacogenomic approach of screening for DNA polymorphisms in gene(s) associated with angiogenesis related pathways that can be exploited to maximize efficacy and reduce toxicity of targeted therapy for kidney cancer. Studies analyzing polymorphisms in vascular endothelial growth factor (VEGF) and VEGF-receptor (VEGFR) suggest that specific single nucleotide polymorphisms (SNPs) in the VEGF gene and the combination of VEGF and VEGF-receptor may be useful as markers to define treatment associated toxicity and overall survival, respectively.

Ovarian cancer is a major cause of mortality among gynecologic malignancies in the United States and Western Europe. The standard of care for patients with advanced disease includes surgical cytoreduction of tumor burden followed by adjuvant chemotherapy with a platinum-based regimen that in most cases includes a taxane. Although response rate with this approach is high (>70 percent), resistance to primary therapy and subsequent recurrence (relapse) is substantial. A further complication is the limited success of second line therapy in patients failing primary therapy or those with recurrent disease.

Using high throughput sequencing strategies, we sought to identify genes that are deregulated in ovarian cancer and contribute to failure of adjuvant treatment or disease recurrence following an initial complete response. Our preliminary studies have identified a subset of genes that can distinguish tumors that respond well to therapy and those that potentially lead to early relapse or recurrence. Following validation of these genes in a larger patient cohort, we plan to carry out prospective clinical trials using the gene signature to predict treatment failure or recurrent disease. Results from these studies could allow us to offer alternate therapeutic strategies to patients with resistant or recurrent disease.

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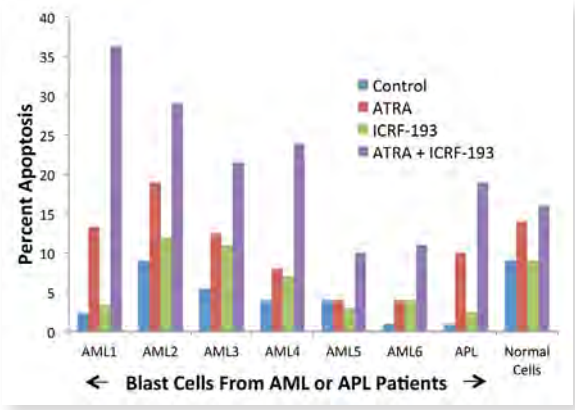


**Figure 1:** Preclinical Studies in AML Evaluating Response of Patient Blast Cells to the Combination of ATRA and ICRF-193.

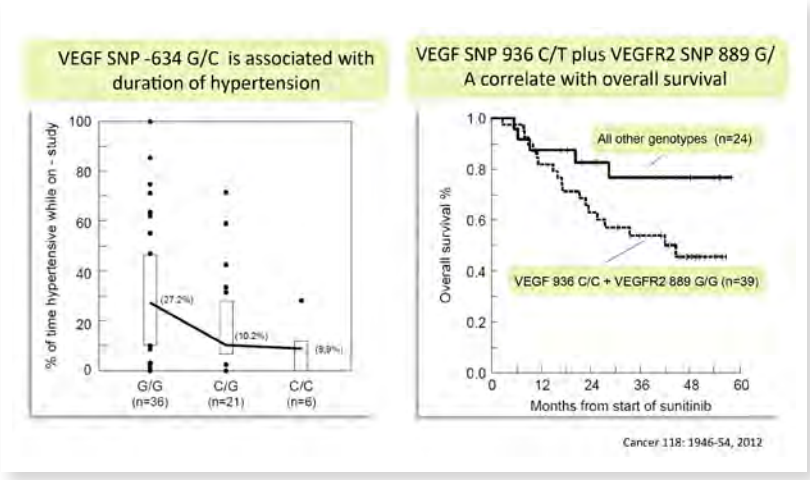


**Figure 2:** Association of VEGF and VEGFR2 SNPs with Toxicity (P = .01) and Overall Survival (P = .03) in Renal Cell Carcinoma Patients Treated with Sunitinib.

# Targeted Folate Receptor Therapy for Ovarian Cancer

## *The PRECEDENT Study*

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Epithelial ovarian cancer is the second most common gynecologic malignancy in the United States.[1] The combination of aggressive surgery, platinum-based chemotherapy, intraperitoneal chemotherapy and the development of new drugs has resulted in a median survival of approximately five years in women with advanced ovarian cancer.[2] When patients become resistant to platinum, response rates are less than 20 percent and overall survival (OS) is less than one year [3]. The development of new drugs is needed, but until recently, no clinical trial has generated any advantage over single agent therapy.

Folate is a vitamin required for DNA replication and cell division. Folate receptor (FR) is strongly expressed in many cancers, including over 80 percent of epithelial ovarian cancers but not in normal tissues, making FR an excellent molecular candidate for targeted cancer therapy.[6] Further, FR expression appears to be a negative prognostic factor in ovarian cancer patients and may allow targeting of cells that are resistance to conventional chemotherapy.[4, 5]

The therapeutic agent vintafolide is a folate-chemotherapy conjugate designed to deliver desacetylvinblastine monohydrazide (DAVLBH) directly to FR-expressing cells while minimizing exposure of vintafolide to non-FR-expressing cells.[6] Normally, DAVLBH is so toxic that it cannot be used systemically. However, it can be conjugated with folate in such a way that the drug is only active when taken up into the cell and the linkage is broken by the lower intracellular pH. Toxicity from this agent is minimal due to nonspecific hepatic breakdown resulting in constipation.

We conducted the first randomized, open label, international phase II clinical trial with this compound in the PRECEDENT trial comparing vintafolide in combination with pegylated liposomal doxorubicin (PLD) versus PLD alone, in women with platinum-resistant recurrent ovarian cancer.[7] The primary objective was to compare the PFS population of patients with measurable disease, and results were statistically significant (HR=0.626; p=0.031). Previous studies suggested patients in whom all lesions expressed the folate receptor by scan had the best clinical response [8] and this hypothesis was supported by results from the PRECEDENT trial. In this group, the hazard ratio for disease progression was 0.381 (p=0.013) resulting in a median PFS increase from 1.5 to 5.5 months. This is the first randomized trial to show a significant benefit to combination chemotherapy in platinum resistant ovarian cancer.[7]

Based on the success of the randomized phase II trial, the PROCEED trial has been launched as an international phase III approval trial for vintafolide in women with FR-positive ovarian cancer by etrafolatide scan. The trial will be conducted in approximately 600 participants, with a primary objective to compare PFS between the study arms in FR-positive participants.

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