



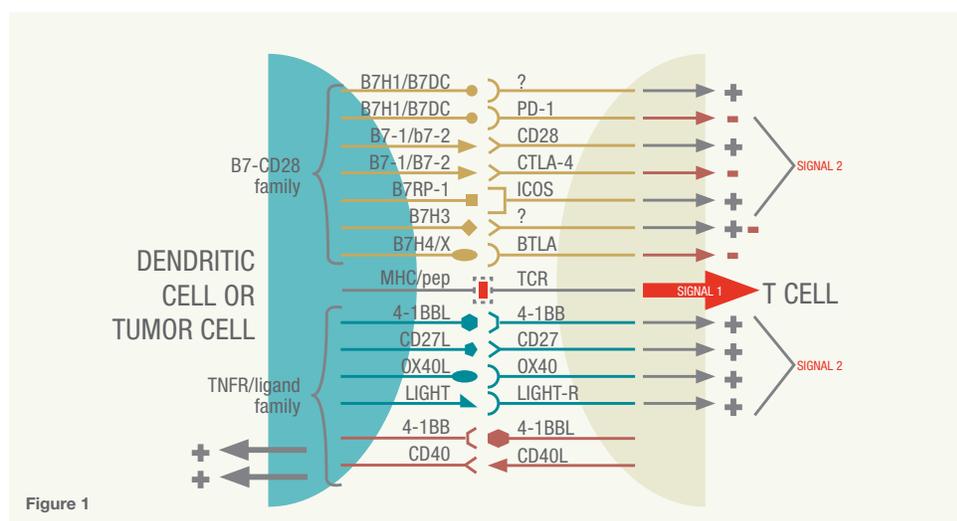
Current Updates in Immunotherapy



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.

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

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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.

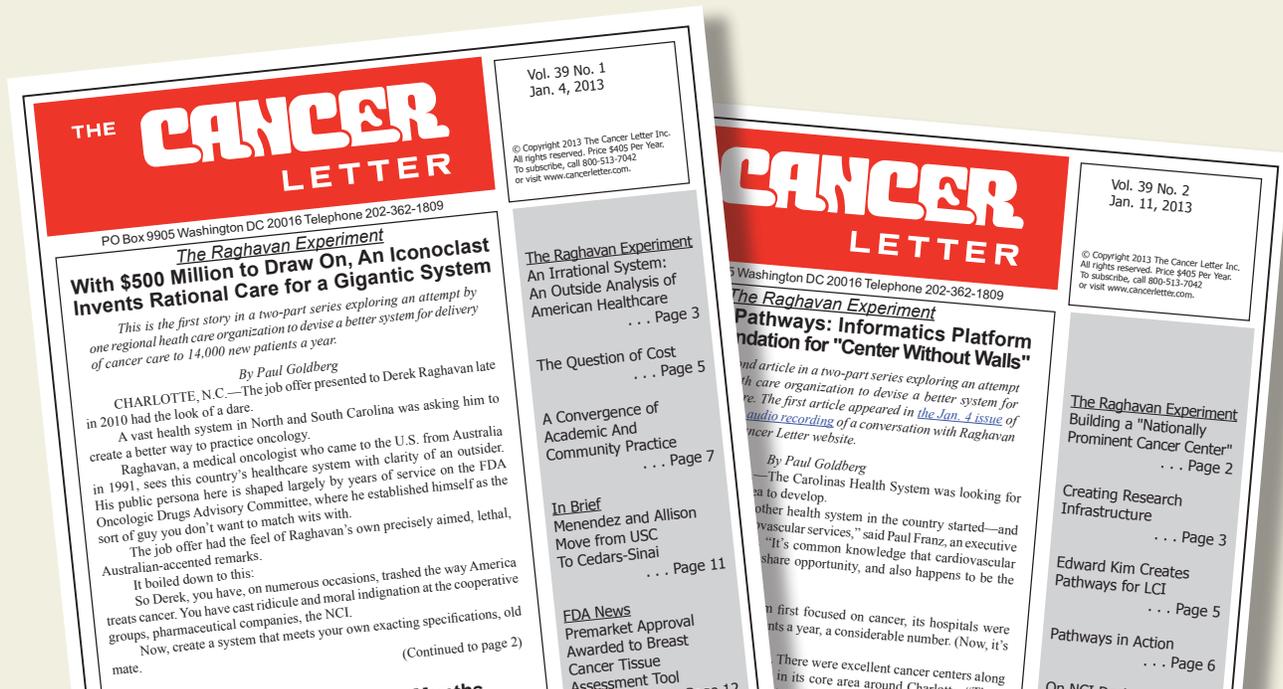
We were very gratified to see the recent coverage of our new research and administrative headquarters along with our academic and clinical programs in two back-to-back issues of *The Cancer Letter*, and I thought you might be interested to read an independent view of our work. Paul Goldberg, a highly 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*.



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Creating Clinical Excellence in Patient Care and Biomarker Driven Research



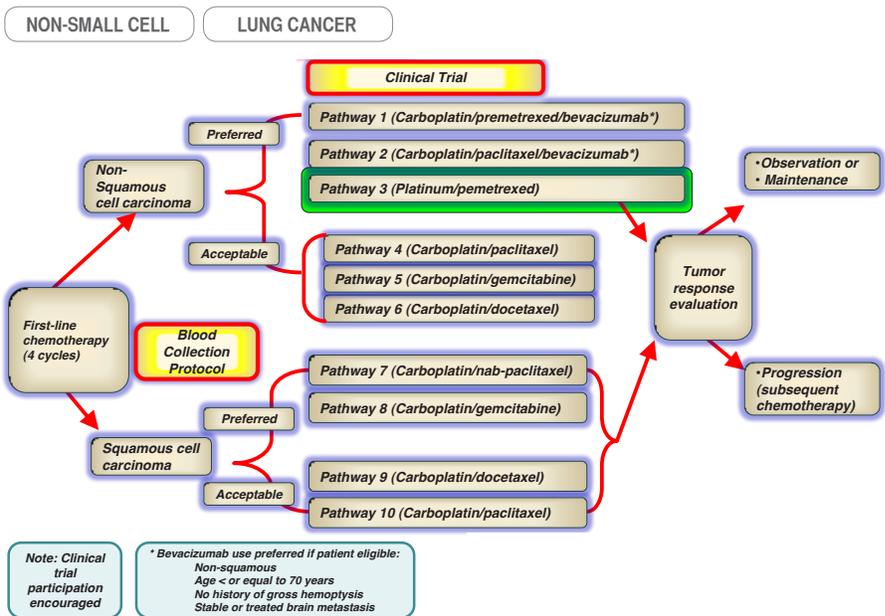
Edward S. Kim, MD (left)
 Chair of the Department of Solid Tumor
 Oncology and Investigational Therapeutics

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.

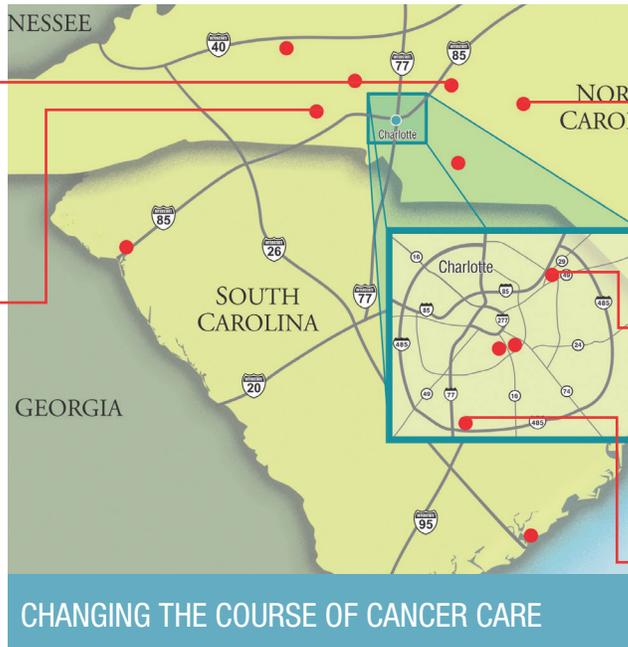
The relationship between Levine Cancer Institute, CMC-NorthEast and the other member institutions located throughout the Carolinas brings increased access to cancer specialists, research and innovative programs and services to patients closer to where they live.



CMC-NorthEast



CMC-Lincoln



Stanly Regional Medical Center



CMC-University



CMC-Union

Advances in Glioblastoma

Updates from Society of Neuro-Oncology 2013



Ashley Sumrall, MD (*left*)
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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.

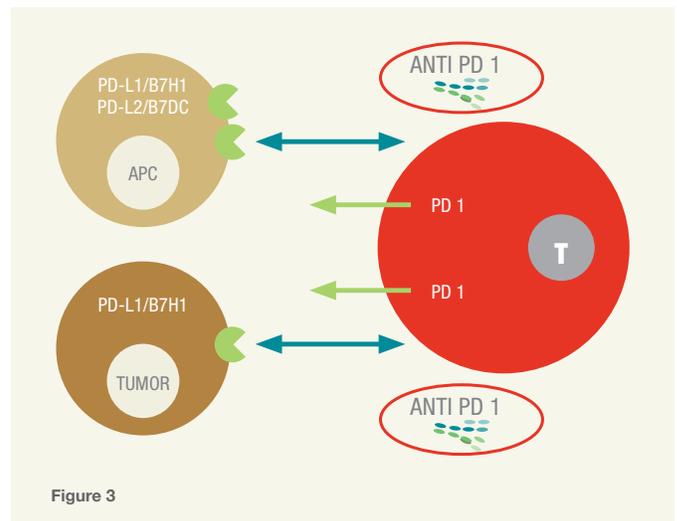
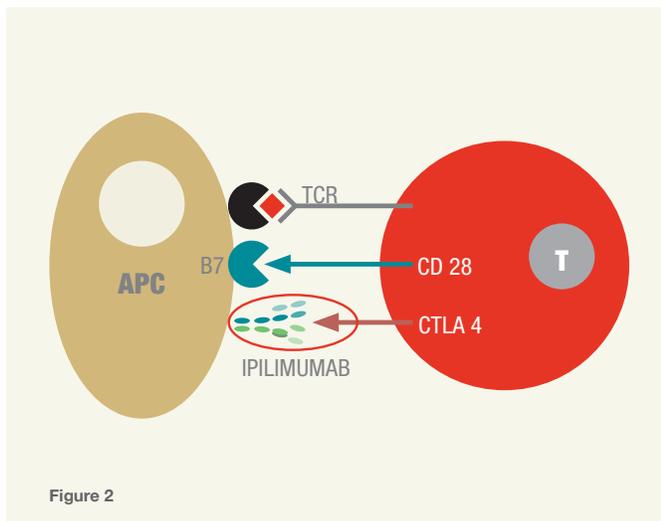
A nonrandomized, phase II study from Duke followed 75 patients with newly-diagnosed glioblastoma who received concurrent chemoradiotherapy and bevacizumab. Median overall survival (as measured from time of enrollment) was 21.2 months and median progression-free survival topped 14 months (95 percent CI: 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

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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 (dermatitis, 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



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Steve Riggs, MD (*right*)
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John Mahoney, MD (*left*)
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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 practitioners (2). In this study, men with chemo-naïve 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



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Reza Nazemzadeh, MD (right)
Medical Oncology



Stuart Salmon, MD (left)
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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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