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S•P•O•H•N•C
A PROGRAM OF SUPPORT
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Personalized Cancer Therapy

Jeffrey Myers, MD, PhD, FACS

For a patient facing treatment or having faced treatment of head and neck cancer, the rapidity with which new information comes out through the many forms of media and social media today, must be overwhelming. The multitude of media and social media formats reporting new advances from a variety of sources can at times provide hope, confusion, and make one question why their own physician didn't offer a certain type of treatment to them. Furthermore, there are few trusted reference sources to go to in order to verify or clarify, what one has read. There has been much written in recent years about Personalized Medicine, Personalized Cancer Therapy, Precision Medicine and Precision Cancer Care. While these terms have specific if somewhat overlapping definitions, their names can be very confusing and can lead patients to ask questions like, "isn't all treatment personalized?", "why didn't my doctor mention Personalized Cancer Therapy to me?", "Was the treatment I received not "precise?" It is my intention that this article will address these questions by precisely defining the terms of Personalized and Precision Treatment, and to place them in a greater context of how cancer treatment decisions are made.

Historically, as will be reviewed in greater detail, the histology (appearance of the cancer under a microscope), primary site of origin of the cancer (location), and stage (tumor size and whether it has spread to lymph nodes or other organs) as well as the patients overall health and views on treatment have been the major factors in treatment selection. Today, after a decade of advances in technology that have led to a much clearer picture of the molecular changes underlying the development of cancers, precise tests can identify specific molecular changes that lead to a cancer's aggressive growth and can also predict the ability of a cancer to respond to a specific treatment. Personalized or Precision cancer therapy is a treatment strategy centered on the ability to predict which patients are more likely to respond to specific cancer therapies based upon specific molecular markers in their cancer.

How Are Cancer Treatment Decisions Made?

Traditionally and even today, after the advent of molecular testing; 1) tumor histology, 2) primary tumor site and 3) stage are the major factors used for treatment selection.

Cancer Diagnosis:

The histology of the cancer is related to the cell of origin from which the cancer arose, and is assessed by a trained pathologist who provides the tissue diagnosis based on a biopsy or removal of a piece of a tumor for the purpose of diagnosis. More and more, biopsies are being performed less invasively using a small needle in a procedure called fine needle aspiration (FNA) biopsy. This provides abnormal cells that are placed on a slide, fixed, and stained, and a cytologist (a specific type of pathologist) makes the diagnosis after viewing the cells using a microscope. FNA biopsies of lymph nodes in the neck, the salivary glands, and thyroid are very commonly practiced today as they are efficient, reliable, cost-effective, and can reach areas that are less accessible to other office based methods of biopsy. Given that some cancers in the head and neck such as salivary tumors and sarcomas are rare and of multiple types, an accurate diagnosis, critical for selecting the proper treatment is based on the training, experience, and sub-specialization of the cytologist/pathologist. Given that these types of cancers are rarely seen in smaller hospitals, referral and reanalysis by subspecialty pathologists with more regular experience diagnosing these tumors is highly recommended. In our hospital, the UT MD Anderson Cancer Center, there is typically a 25-30% rate in change in diagnosis from the diagnosis given by the outside pathologist. The World Health Organization (WHO) has worked with the International Agency for Research on Cancer (IARC) to optimize the pathologic and genetic classification and grading of all human cancers to standardize the diagnostic criteria worldwide. This book is updated frequently and distributed to hospitals and pathologists throughout the world. http://whobluebooks.iarc.fr/

Primary Tumor Site

Where a tumor originates has a major impact on what type of treatment should be used for several reasons. One is related to histology as discussed above. For example, cancers of the mouth or oral cavity, including the tongue, cheek, palate, and floor of the mouth most often arise from the squamous lining cells of these

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structures, giving rise to squamous cell carcinomas. In addition, the structures surrounding the cancer's primary site can be damaged by the cancer treatment; for example radiation treatment of oral cavity cancers can be damaging to the blood supply of the jaws and teeth so that surgery is usually recommended for cancers in the mouth. In contrast, cancers of the larynx (voice box) are also most often squamous cell carcinomas, and are typically treated with radiation or chemoradiotherapy to preserve the larynx so patients can speak, swallow, and breathe as normally as possible.

The other major sites in the head and neck include the oropharynx, where the tonsils and tongue base are located; the hypopharynx (throat) which surrounds the larynx; the nasopharynx, behind the nose, and the nose and sinuses. The salivary glands both major and minor, the thyroid, and the skin are other sites from which cancers can develop, and each of these have unique considerations for treatment selection.

Cancer Staging

Cancer staging provides doctors and patients with a way of determining the extent of the cancer a patient has, and includes the initial tumor or primary tumor (T stage) where the cancer started and adjacent structures that the tumor can invade, lymph nodes to which the tumor can spread (N stage), as well as other organs outside of the head and neck region to which a cancer might metastasize (M). The most widely accept ways of staging cancers incorporates all of these characteristics, T, N, and M staging to come up with an overall stage from Stage I to Stage IV, with lower numbers reflecting the best prognosis. The most widely accepted and practiced staging system used today is from the American Joint Committee on Cancer or AJCC. https://cancerstaging.org/About/what-is-the-ajcc/Pages/whatisajcc.aspx. The AJCC publishes, the Cancer Staging Manual and Cancer Staging Atlas, which is currently in its 8th Edition, and is "recognized as the authoritative guide for cancer staging information and is used by tens of thousands of medical professionals everyday."

The AJCC stage I to IV system gives a relatively clear idea of a patient's prognosis, with Stage I and II cancers being associated with better survival outcomes than patients with Stage III or IV cancers. This uniform language for communication about the patient's extent of the cancer enables the doctors to select appropriate treatments and to explain the treatment options to their patients.

Treatment Selection:

With accurate primary site, diagnosis, and staging information in hand, a physician is ready to discuss treatment options with the patient. Traditionally, there have been three major treatment options for treating cancers; 1) Surgery, 2) Radiation, and 3) Medical Treatment including chemotherapy, molecularly targeted therapies, and immunotherapies. Sequential and concurrent combinations of any or all of the three major options are also often recommended. A few principals guiding treatment selection include:

1) Selecting the minimal number of modalities needed to effect a cure. As each treatment modality is associated with side effects, both predictable and unpredictable; it is desirable to use the fewest modalities needed to cure a

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patient. Often Stage I and II tumors can be effectively cured with a single modality or combination of two treatments, while Stage III and Stage IV tumors often require treatment with multiple or all available modalities.

2) Selecting the modality (ies) to be used primarily should occur after review by a Multi-disciplinary discussion such as a regular Tumor Board or planning conference attended by practitioners of Head and Neck Surgery, Radiation, and Medical Oncology-and ideally Speech Pathologists, Dental Oncologists, Radiologists, and Pathologists as this provides the best oncologic and functional outcomes for patients.
3) Patients' preferences are the highest priority for choosing the best treatment. While oncologists (Doctors who specialize in treating patients with cancer) are typically oriented to effecting cures and a hierarchy of priorities organized around 1) cure, 2) preservation of normal functions such as speech and swallowing, and 3) cosmetic concerns, patients may have different priorities which place quality of life above quantity of life, and it is important that a frank discussion be had between the oncologist, the patient and their families to choose the treatment for the particular patient.

In order to provide the evidence about the success of different treatments available to physicians and patients so that they can select the most appropriate treatment, the National Comprehensive Cancer Network, NCCN, has developed guidelines about the best way to diagnose, stage, treat, and follow patients with cancer of any type, and has made these available to the public (https://www.nccn.org/patients/). In the case of head and neck cancers; experts from head and neck surgery, head and neck oncology, head and neck radiation oncology, pathology, radiology, and statistics have met and reviewed the best available data on treatment outcomes and developed guidelines for the management of head and neck cancers of each different histology, location, and stage.

It should be noted that these guidelines are, as the name suggests, just "guidelines", based on the best evidence for an "average patient". However, no patient is "average", and the special circumstances of each patient's age, overall physical condition, cultural and spiritual values, motivation and desires need to be considered and individualized treatment decisions need to be agreed upon by the patient and the physician. Nevertheless, head and neck oncologists are taught the NCCN guidelines for cancer management and should follow them to the degree that it's possible. More and more, physicians are encouraged to follow the NCCN guidelines, and researchers, hospitals and insurance companies are defining healthcare "quality" metrics that encompass the use of guidelines to ensure that the public will be offered the most effective value based care.

Personalized Cancer Therapy

While most would agree that the care of each cancer patient should be individualized based on the best available evidence summarized in the NCCN guidelines, a newer concept, called Personalized or Precision Cancer Treatment, has emerged as molecular testing of patients' cancer has become a mainstream practice over the past several years for patients with specific types of cancers. Personalized cancer therapy is a treatment strategy centered on the ability to predict which patients are more likely to respond to specific cancer therapies, based on abnormalities in specific genes and the proteins that they encode that are identified through molecular testing. While multiple parallel fields of research have converged over the past decade, to make personalized cancer therapy a reality, the ability to sequence all the genes in any given cancer based in a technology known as Next Generation Sequencing, NGS, has really enabled rapid progress in this field. At the same time, investigators have developed drugs which can target specific genetic defects that drive the growth of some cancers. In the case of melanoma, this type of Personalized or Precision Treatment has become a standard of care that has been incorporated into the NCCN guidelines for treatment of that cancer type. For patients with a melanoma that cannot be surgically removed (un-resectable) or is metastatic throughout the body, that has a mutation in the *BRAF* gene, there are oral BRAF inhibitors that are recommended for treatment and have been associated with major responses (shrinkage and even disappearance of tumor) and long disease free intervals. Similarly, many patients with lung cancer have alterations in the *ALK* gene, which can be targeted for treatment leading to a percentage of durable responses.

Personalized
Head and Neck Cancer Therapy

For a variety of reasons, progress in Personalized Cancer Therapy for cancers of the head and neck has lagged behind the advances made in melanoma and lung cancer. The major reason for this has to do with a relative lack of "targetable" gene alterations in this tumor type. Two landmark publications recently used whole-exome sequencing and gene copy number analysis to study HNSCC. Known tumor suppressor genes and oncogenes were found to be mutated, including *TP53, PIK3CA, PTEN, HRAS,* and *CDKN2A*. Of particular interest, was the identification of loss-of-function mutations in *NOTCH1*, suggesting that *NOTCH* may act as a tumor suppressor gene rather than as an oncogene, as identified in other malignancies. Given these findings, head and neck squamous cancers seem to have fewer targetable oncogenes amenable to molecular therapies. The Cancer Genome Atlas (TCGA), a major effort by the National Cancer Institute and National Human Genome Research Institute to sequence all the genes in most major cancers recently published results validating these findings. Although the majority of known mutations represent non-targetable tumor suppressor genes, further study of downstream and upstream mediators may help to identify therapeutic targets. Therefore, it is highly likely that in the next few years, molecular tests will be used to identify patients most (or least) likely to respond to specific types of treatment thereby helping us to select more effective treatments and to avoid toxic treatments that are less likely to work for a given patient.

One area of particular promise is in the field of Cancer Immunotherapy, in which patients' immune systems are stimulated

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to attack their cancers. Recent publications have shown that this type of treatment using specific drugs called check-point inhibitors can be very effective in prolonging lives of patients with recurrent and/or metastatic head and neck squamous cell cancers, and that there are specific immune markers that can be identified in the cancers of patients who responded to treatment as compared to non-responders.

The rapid advances in the molecular characterization of head and neck cancers, targeted therapy and immunotherapy provide us with a healthy sense of optimism that Personalized Head and Neck Cancer Therapy will become a reality for many head and neck cancer patients in the next several years.

Editors Note: Dr. Jeffrey N. Myers is a head and neck surgeon, Full Professor, and translational scientist at the University of Texas MD Anderson Cancer Center, where he has been on faculty since 1997. He serves several important roles, including Deputy Chair for Academic Programs and Director of Research for the Department of Head and Neck Surgery, and currently holds the Alando J. Ballantyne Distinguished Chair of Head and Neck Surgery.

Dr. Myers has been a reviewer on several NIH study sections, has been a principle or co-principle investigator on numerous investigator-initiated and cooperative group trials, and has served in several prominent positions on national committees. He was named the President of the American Head and Neck Society in July 2016.

Dr. Myers received his medical (MD) and doctoral (PhD) degrees from the University of Pennsylvania School of Medicine and he then completed his residency training in Otolaryngology-Head and Neck Surgery at the University of Pittsburgh. He subsequently completed fellowship training in Head and Neck Surgical Oncology at the University of Texas MD Anderson Cancer Center in 1997, where he has been on the faculty ever since.

Dr. Myers leads a basic and translational research program that has been funded by several institutional, state and national grants. His primary research interests are in the role of p53 mutation and other genomic alterations in oral cancer progression, metastasis and response to treatment.

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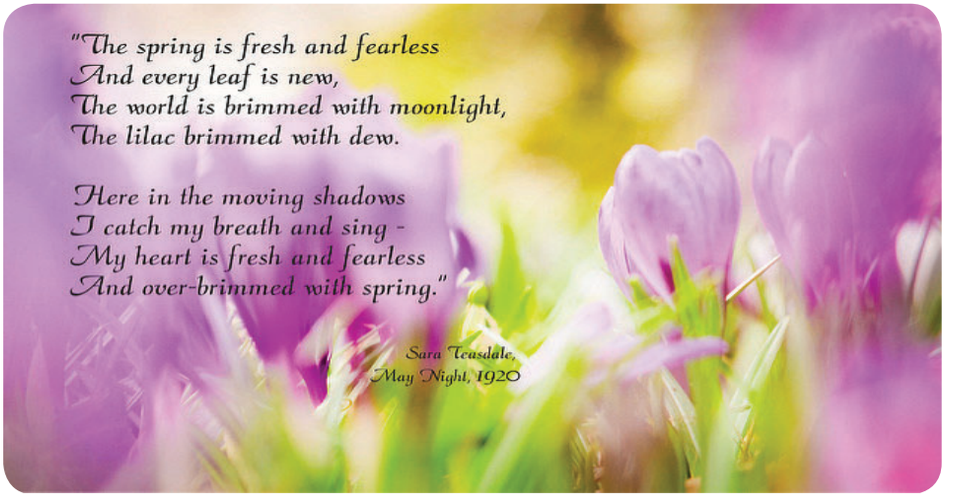

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A Time For Sharing...

SPOHNC Executive Director Mary Ann Caputo and Pro Football Hall of Famer Jim Kelly Provide Information for Those Impacted by Head and Neck Cancer

For more than 25 years, SPOHNC has worked to raise awareness and meet the needs of people living with oral and head and neck cancer through its resources and publications. In April, during Oral, Head and Neck Cancer Awareness Month, we place an even greater emphasis on education about the disease and the unique challenges those impacted face on a daily basis.

Head and neck cancer survivor and Pro Football Hall of Famer Jim Kelly understands these challenges firsthand. He's teamed up with SPOHNC, Merck and other leading cancer organizations to share his personal experience as part of Your Cancer Game Plan, a new awareness campaign focused on tackling the emotional, nutritional and communication needs of those facing cancer. Jim recently sat down with me to discuss his journey. You can also see him share tips on how to remain positive on YourCancerGamePlan.com.

Mary Ann: Jim, thank you for speaking out about your own experience. As you know, the American Cancer Society statistics say that approximately 49,670 Americans are diagnosed with oral, head and neck cancer each year, excluding cancer of the larynx and thyroid. There's a lot of fear and anxiety that comes along with that realization. Tell us your story and what advice would you offer others.

Jim: I was having some tooth issues so, of course, I went to the dentist. And I was thinking, okay, maybe they'll do a root canal or whatever to make me feel better. But my pain increased, my headaches were also getting a lot worse. They extracted some of my teeth, and I had a few root canals. Then they decided to do a biopsy, which came back negative and I thought to myself "thank God." But the pain continued so I underwent a second biopsy, which unfortunately came back positive. I was diagnosed with squamous cell carcinoma – a cancer of the upper jaw. My whole upper jaw was removed. It was pretty challenging, not just physically but emotionally as well.

Through my journey, I've been very blessed to have great support from family and friends. Not everyone has the support of family and friends. Your mind is working all the time, and often the negativity pops in. And you can't have that negativity. You have to be able to talk to somebody. And when the anxiety kicks in you have to be able to surround yourself with people that are willing to make your day better by their presence, by what they say. But the thing is, it's your attitude as well.

Mary Ann: Yes, Jim, we've spoken about this many times. You have a wonderful support system. You have your four F's: your family, your faith, your friends and fans.

People can also come to SPOHNC to speak to others who have traveled a similar journey and who they can relate to. Many patients attend one of SPOHNC's more than 125 chapters that are located throughout the U.S. in multiple cities. We also offer a National Survivor Volunteer Network of volunteers who are matched with patients according to their diagnosis and treatment. Finding others who have walked in your shoes can be helpful to one going through a cancer journey of this magnitude.

Beyond a support network, you also noted the importance of having a positive attitude despite the circumstances. How can people living with head and neck cancer stay strong and keep an optimistic outlook?

Jim: When I was first diagnosed our family motto, 'Kelly Tough,' meant being physically strong; you get knocked down, you get back up, you keep fighting. That's a big part of it. But, it's also about being mentally strong—keeping a positive frame of mind.

My family showed up smiling, not frowning or crying. That kept me going. During treatment, the toughest times for me were when all the visitors left and I was alone. I used those visits and the lingering good feelings I had to re-focus my attention on the days ahead.

Mary Ann: Those are great points Jim; we know firsthand here at SPOHNC in speaking with people living with head and neck cancer the importance of feeling both mentally and physically strong. Another area where people seem to struggle is with communication. It goes without saying — a cancer journey can be a terrible experience for you and your loved ones. You might not be ready to talk right away. When you are, you may not know exactly what to say. People may feel nervous about saying the wrong thing, and decide instead to say nothing at all. Jim, how did you learn to open up? What strategies worked for you that may work for others?

Jim: Communication can be tough, especially for people like me who aren't used to or comfortable openly sharing their feelings. But I'm not like I used to be; hardheaded, a guy who had to have things his way. Now, I'm very coachable. I listen a lot more, and the ego is not as high as it was once.

When I was diagnosed, my biggest concern was how am I going to tell my daughters and how am I going to tell my wife. And then once I did tell them, which was very hard, they had the attitude that, hey, you're not going to fight this alone. We're fighting this together.

Along the way I learned that it's really important to be honest with your loved ones, yourself and your team of doctors. Make sure that you're being open and direct, and in steady communication about how they can help you.

Mary Ann: Jim, thank you again for sharing these valuable tips with our community - any final thoughts?

Jim: I would encourage people to visit www.YourCancerGamePlan.com or join the conversation on Twitter using #CancerGamePlan. There, you can find

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support and resources, including more of my tips on how to remain positive as well as healthy recipes for those with head and neck cancer.

Finally, I want to make sure people understand that they can help others by making a difference today for someone who is fighting for their tomorrow.

For more information about Your Cancer GamePlan, please visit our website at spohnc.org.

Easter and Passover Delights from Eat Well Stay Nourished A Recipe and Resource Guide For Coping With Eating Challenges

Compiled and Edited by Nancy E. Leupold, Survivor, Founder & President Emeritus

Cheesy Ham and Asparagus Bake

(from Volume One)

1 ½ c. cooked ham – chopped
1 medium onion, chopped
1/4 c. bell pepper, chopped
1 pkg. frozen asparagus or broccoli cuts
8 eggs or 2 c. fat free cholesterol free egg product
2 c. milk
1 c. all purpose flour
1/4 c. parmesan cheese
2 Tbsp. butter or margarine
½ tsp.salt
½ tsp. pepper
½ tsp. fried tarragon laves
1 c. shredded cheddar cheese

Preheat oven to 425 degrees. In small saucepan, sauté onions and bell pepper in butter. Grease bottom and sides of 13 x 9 baking dish with shortening or baking spray. Sprinkle ham, onion, bell pepper and asparagus in baking dish. Beat eggs, milk flour, parmesan cheese, salt, pepper and tarragon with fork until smooth. Pour over ham mixture. Bake uncovered about 20 minutes or until knife inserted in center comes out clean. Sprinkle with cheddar cheese. Bake an additional 3 to 5 minutes or until cheese is melted. Let stand 5 minutes before cutting. Yields 6 servings. *418 calories/serving*.

~ Rita Burfitt, NJ

Apple Cake

(from Volume Two)

4 c. apples – peeled, quartered and diced
2 beaten eggs
1 c. Crisco oil
2 c. sugar
2 c. flour
1 tsp. cinnamon
2 tsp baking soda
1 tsp. salt
1 c. chopped nuts (optional)

In medium bowl, mix apples with eggs, Crisco and oil. Combine flour, cinnamon, baking soda and salt. Add dry mixture to apple mixture. Grease and flour 9 x 12 pan and pour mixture in. Bake at 350 degrees for 55 – 60 minutes or until knife comes out clean. Serves 14 to 16. *369 calories/serving*.

~ Marge Robertson, NY

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HEAD AND NECK CANCER NEWS

Immunotherapy Making Its Mark on Head and Neck Cancer

Mar 22, 2017 - Following the approval of 2 immunotherapy agents, pembrolizumab (Keytruda) and nivolumab (Opdivo) for the treatment of patients with head and neck cancer (HNC) over the last 6 months, immunotherapy is making its mark on the treatment paradigm for HNC.

Due to the responses seen with these 2 agents, immunotherapies are being investigated further in the treatment of HNC.

"Immunotherapy is a very potent treatment for some patients. In a way it shows you that we're probably just scratching the surface with [immunotherapy treatment for HNC]," Tanguy Seiwert, MD, said during a presentation at the 1st Annual International Congress on Immunotherapies in CancerTM, hosted by the Physicians' Education Resource (PER).

Findings from the KEYNOTE-012 trial led to the approval of pembrolizumab in patients with recurrent head and neck squamous cell carcinoma (HNSCC). The overall response rate was 18% with only 1 patient experiencing a complete response.1 However, about 50% of patients, both HPV-positive and HPV-negative, experienced a decrease in their target lesions.

"I would like to point out that response is a terrible, terrible outcome measure for immunotherapy. In the end, what we really care about with immunotherapy is overall survival [OS]," commented Seiwert, associate program director of the Head and Neck Cancer Program, and assistant professor of medicine, The University of Chicago Medicine. "Many patients have prolonged stable disease and that likely contributes signicantly to the strong OS signal that we oftentimes see."

The phase III CheckMate 141 trial, which Seiwert said was "arguably the most important study in the field," showed a difference in OS that is more revealing of outcome measures in immunotherapy. CheckMate 141 investigated nivolumab monotherapy in the second-line setting versus investigator's choice of chemotherapy in patients with recurrent or metastatic HNSCC and demonstrated a median OS of 7.5 (95% CI, 5.5-9.1) versus 5.1 months (95% CI, 4.0-6.0) with standard therapy (P = .0101).2 The 1-year OS rate was 36% with nivolumab versus 16.6% with standard therapy. Alternatively, the response rate was 13.3% with nivolumab compared with 5.8% in the standard therapy arm.

"The response rate wasn't that impressive, but the overall survival data are stunning. And that's again an example of how wonderfully these drugs work," Seiwert said.

Following the responses seen in these 2 studies of PD-1 inhibitors, immunotherapy agents are being considered in the frontline, including in combination regimens, which Seiwert believes are promising. One such combination is durvalumab (MEDI4736), a PD-L1 inhibitor, and tremelimumab, an anti–CTLA-4 agent, which was compared against durvalumab or the EXTREME trial regimen of cetuximab (Erbitux) and platinum-based chemotherapy in the phase III KESTREL trial.

Other first-line combination studies of interest in HNC include the KEYNOTE-048 study, which is looking at pembrolizumab and chemotherapy versus pembrolizumab monotherapy or the EXTREME regimen (NCT02358031); the CheckMate 651 study of ipilimumab (Yervoy) and nivolumab versus EXTREME (NCT02741570); and the CheckMate 714 study exploring ipilimumab and nivolumab versus nivolumab as a single agent (NCT02823574).

Preliminary results looking at the combination of lirilumab, an anti-KIR agent, and nivolumab in a phase I/II study were presented at the 2016 SITC Annual Meeting. The combination showed an objective response rate (ORR) of 24.1% versus an ORR of 13.3% seen with nivolumab monotherapy in the CheckMate 141 trial.2,3 The OS at 1 year was 60% with the combination compared with 36% for nivolumab monotherapy. Among patients with PD-L1 expression in the tumor cells of ≥50%, the ORR was 57.1% with lirilumab and nivolumab versus 36.8% with nivolumab alone. Seiwert hypothesized that KIR was among a number of targets, also including CTLA-4, IDO, and OX40, that are more active in hot tumors.

In discussing which patients should receive immunotherapy treatment, Seiwert looked to various biomarkers currently under investigation for their predictive or prognostic association to immunotherapy response. The KEYNOTE-024 trial looking at pembrolizumab versus chemotherapy in patients with non–small cell lung cancer changed the eld of PD-L1 testing, according to Seiwert. There was a significant difference in progression-free survival (PFS) and OS rates noted in patients with PD-L1 expression of ≥50% on the tumor cells.4 This can be translated into HNC, and notably, the KEYNOTE-048 trial of patients with recurrent or metastatic HNSCC will include a PD-L1–positive subgroup as part of its investigation.

"While I do have my doubts about how perfect PD-L1 testing is, I do believe it plays a role for enrichment," Seiwert commented.

An interferon-gamma (IFN-γ) signature showed significant association with overall response (P = .005) and PFS (P <.001) in an analysis of PD-L1–positive patients from the KEYNOTE-012 trial.5 There was also a very high negative predictive value for patients with non–IFN-γ–inflamed tumors who did not receive benefit from pembrolizumab, which would prove useful in identifying which patients should not receive anti–PD-1 therapy. Of great interest are the patients with inflamed tumors who do not benefit from the treatment. Perhaps they could be converted into responders through combination therapies, Seiwert pondered.

"None of these biomarkers are perfect. I think we need a bit more time to fully understand this, but these are biomarkers that are potentially helpful and might outperform PD-L1 testing in the near future," Seiwert said.

HAPPY SPRING!!

Photo courtesy of PJ Jordan

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HEAD AND NECK CANCER NEWS

Targeting cancer stem cells improves treatment effectiveness & prevents metastasis

03/09/2017 - Targeting cancer stem cells may be a more effective way to overcome cancer resistance and prevent the spread of squamous cell carcinoma — the most common head and neck cancer and the second-most common skin cancer, according to a new study by cancer researchers at the UCLA School of Dentistry.

Head and neck squamous cell carcinoma is a highly invasive form of cancer and frequently spreads to the cervical lymph nodes. Currently, cisplatin is the standard therapeutic drug used for people with HNSCC. Yet, more than 50 percent of people who take cisplatin demonstrate resistance to the drug, and they experience a recurrence of the cancer. The five-year survival rates remain sorely low and researchers still don't understand the underlying mechanisms behind head and neck squamous carcinoma. Therefore, said UCLA cancer biologist Dr. Cun-Yu Wang, who led the study, there's an urgent need to understand why people with this type of cancer are resistant to therapy and to develop new approaches for treating it. Wang's research is published online today in the peer-reviewed journal Cell Stem Cell.

Cancer stem cells are known to be responsible for tumor formation and development; they also self-renew and tend to be unresponsive to cancer therapy. These cells have been found in head and neck squamous cell carcinoma. Given the unique challenges that cancer stem cells pose for oncologists, it remains unclear what the optimal therapeutic strategy is for treating HNSCC.

To address this, Wang, who holds the Dr. No-Hee Park Endowed Chair in Dentistry at UCLA and holds a joint appointment in the UCLA Department of Bioengineering, and his research team first developed a mouse model of head and neck squamous cell carcinoma that allowed them to identity the rare cancer stem cells present in HNSCC using in vivo lineage tracing, a method to identify all progeny of a single cell in tissues.

The researchers found that the cancer stem cells expressed the stem cell protein Bmi1 and had increased activator protein-1, known as AP-1, a transcription factor that controls the expression of multiple cancer-associated genes. Based on these new findings, the UCLA team developed and compared different therapeutic strategies for treating head and neck squamous cell carcinoma. They found that a combination of targeting cancer stem cells and killing the tumor mass, consisting of high proliferating cells, with chemotherapy drugs resulted in better outcomes.

The team further discovered that cancer stem cells were not only responsible for squamous cell carcinoma development, but that they also cause cervical lymph node metastasis.

"This study shows that for the first time, targeting the proliferating tumor mass and dormant cancer stem cells with combination therapy effectively inhibited tumor growth and prevented metastasis compared to monotherapy in mice," said Wang, who is a member of the UCLA Jonsson Comprehensive Cancer Center and of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA. "Our discovery could be applied to other solid tumors such as breast and colon cancer, which also frequently metastasizes to lymph nodes or distant organs."

"With this new and exciting study, Dr. Wang and his team have provided the building blocks for understanding the cellular and genetic mechanisms behind squamous cell carcinoma," said Dr. Paul Krebsbach, dean of the UCLA School of Dentistry. "The work has important translational values. Small molecule inhibitors for cancer stem cells in this study are available or being utilized in clinical trials for other diseases. It will be interesting to conduct a clinical trial to test these inhibitors for head and neck squamous cell carcinoma."

Additional authors of the study include Demeng Cheng, first author and postdoctoral scholar in Wang's lab; Mansi Wu, Yang Li, Dr. Insoon Chang, Yuan Quan, Mari Salvo, Peng Deng, Dr. Bo Yu, Yongxin Yu, Jiaqiang Dong, John M. Szymanski, Sivakumar Ramadoss and Jiong Li who are all from the laboratory of molecular signaling in the division of oral biology and medicine at the UCLA School of Dentistry.

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