SOAP is dedicated to promoting awareness for all cancers, supporting cancer patients and survivors, and providing opportunities for students interested in oncology. SOAP hopes to garner support for oncological research and unite those who are affected by cancer through advocacy, education, and community involvement.
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Free to Breathe 5k -- 11/26
SOAP Christmas Party -- 11/21

VOLUNTEER OPPORTUNITIES
In Their Shoes 5k
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Emerging Treatment: Personalized Vaccine for Renal Cell Carcinoma

Written by: Bayleigh Carver, Pharm.D. Candidate 2022

Vaccines are widely accepted as a method of preventative care to ensure communities are protected against infectious diseases based on herd immunity. For example, patients who receive the seasonal influenza vaccination all receive the same 4 strains of the inactivated influenza virus. However, what if vaccines could be personalized to each individual patient? Furthermore, what if these vaccines could be personalized to a cancer patient’s tumor cells to activate the patient’s own immune system to attack those cancer cells? This is exactly what Dr. Braun, Dr. Chouein, and Dr. Ott are researching in hopes of discovering a new approach to treating patients with high-risk renal cell carcinoma (RCC).1

A neoantigen vaccine stems from the same basic principle of currently utilized vaccines: activating the immune system against an antigen. However, instead of administering the vaccine to a healthy individual as preventative care, NeoVax is a therapeutic vaccine under investigation for patients with recurrent RCC. Rather than activating the immune system against a foreign invader, therapeutic cancer vaccines aim to activate the immune system against cancerous tumor cells. Genetic mutations that lead to tumor growth and rapid cancer cell division also lead to the formation of cancer-specific proteins, also known as neoantigens.2 Since these neoantigens are only present on cancerous cells, the vaccine is able to activate the immune system to specifically target those cells. These vaccines are created by taking a sample of the patient’s tumor cells to determine which neoantigens are present.3 This is the personalized component of the vaccine; each patient will present with different mutations that lead to the production of different cancer-specific proteins. The resulting vaccine is designed to activate the immune system specifically against the neoantigens that are present on the patient’s cancer cells.

As the eighth most common cancer diagnosed in adults in the U.S., kidney cancer has a substantial prevalence with an estimated 73,820 new cases in 2019. The 5-year relative survival rate is highly dependent upon the stage of cancer at diagnosis. Once cancer has spread beyond the kidney, it is considered regional and encompasses stage III and some stage IV cancers. Regional kidney cancer has a 5-year relative survival rate of 69% which drops to a dismal 12% for those with distant kidney cancer, such as those that have spread to the lungs or bone.4 Further, RCC is the most lethal of the urologic malignancies, with a 20% to 40% recurrence rate after nephrectomy.5 Therefore, due to the poor prognosis of advanced kidney cancer and high rate of recurrence, a vaccine that has the possibility of treating this patient population has the potential to substantially advance treatment of this important disease.

Currently, a phase I clinical trial organized by Dana-Farber Harvard Cancer Center is researching NeoVax in combination with ipilimumab; therefore, the vaccine is being tested for safety and appropriate dose.6 Ipilimumab is an immune checkpoint inhibitor utilized to treat other solid tumors, such as melanoma. Immune checkpoint proteins operate by keeping the immune system in check, i.e. down-regulating its activity by inhibiting T-cell proliferation and interleukin production.7 Drugs that are able to block these proteins allow the immune system to function at full capacity. In the case of ipilimumab, the immune checkpoint protein cytotoxic T-lymphocyte associated protein 4 (CTLA-4) is inhibited.

In this study, the patients will first undergo surgery to remove the primary kidney tumor as per standard of care. Samples will be taken from the tumor and analyzed to determine the neoantigens that have the highest chance of provoking a response by the immune system. Once determined, the neoantigen peptides will be
combined with poly-ICLC to form the NeoVax vaccine. According to the National Cancer Institute, poly-ICLC is a synthetic complex that may stimulate the release of cytotoxic cytokines and increase tumoricidal activities. Poly-ICLC is an experimental drug and has not been approved for use. NeoVax will be administered on days 1, 4, 8, 15, and 22. Ipilimumab will be administered under the skin within 1cm of each Neovax administration. NeoVax will be administered again on days 78 (week 12) and 134 (week 20) as part of the boost phase. The primary outcome measure will be the number of participants with dose-limiting toxicity experienced within 49 days of therapy. Secondary outcome measures are the participants’ immune response to the vaccine (NeoVax induced INF γ T-cell response) and number of participants alive at 2 years.

NeoVax is an example of modern medicine characterized by moving away from the idea that all patients should be treated with the same cytotoxic therapy, to a more personalized approach, in which therapy is targeted to patient-specific factors. Since NeoVax is currently being tested for safety and therapeutic dose in early phase trials, more research is needed to be able to utilize this technology in clinical practice; however, neoantigen vaccines have the potential to personalize medicine to a greater extent by recognizing and targeting a variety of genetic mutations between patients.

References:
Entrectinib (Rozyltrek): Targeting a Key Genetic Driver of Cancer
Written by: Julia Kim, Pharm.D. Candidate 2021

On August 15th, 2019, the Food and Drug Administration (FDA) approved entrectinib (Rozyltrek) for a tissue anagistic indication, the third drug to receive such an indication, following pembrolizumab and larotrectinib. These approvals represent a new paradigm in cancer treatment, where treatments are determined by the genetic makeup of the tumor, rather than the site of the tumor. Entrectinib was granted accelerated approval for adult and pediatric patients 12 years and older who have solid tumors with the neurotrophic tyrosine receptor kinase (NTRK) gene fusion that are metastatic or unresectable. Patients must have progressed following previous treatment or have no effective alternative treatments available. Additionally, entrectinib was approved for the treatment of metastatic non-small cell lung cancer (NSCLC) in adults whose tumor is ROS1 proto-oncogene receptor tyrosine kinase (ROS1) gene positive.

Entrectinib is an orally available small molecule tyrosine kinase inhibitor (TKI) of NTRK 1/2/3, ROS1, and anaplastic lymphoma kinase (ALK). NTRK gene fusions lead to the production of tropomyosin-related kinase (TRK) proteins that can be a primary driver of various cancers. NTRK gene fusions are more common among rare cancer types such as mammary secretory carcinoma, mammary analog secretory carcinoma, and congenital fibrosarcoma, but are far less common in cancer types such as sarcomas, gastrointestinal tumors, and lung cancer. ROS1 and ALK are established therapeutic targets in NSCLC, with a prevalence of 1-2% and 3-4%, respectively.

The results from three clinical trials were the basis of entrectinib’s approval for solid tumors with NTRK fusions: ALKA, STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267). The patients were tested for the NTRK gene fusion prior to enrollment using nucleic acid-based tests. The ALKA trial was an open label, dose-escalation trial that studied patients with TrkA/B/C, ROS1, or ALK gene rearrangements in Italy receiving entrectinib intermittently and continuously. STARTRK-1 was an open-label, dose escalation that studied patients with NTRK1/2/3, ROS1, or ALK gene rearrangements in the United States and South Korea receiving entrectinib on a daily continuous dose. STARTRK-2 was an open-label basket trial conducted in patients with NTRK1/2/3, ROS1, or ALK gene rearrangements.

Fifty-four adult patients were analyzed with advanced or metastic solid tumors harboring NTRK gene fusions in a pooled analysis of the three clinical trials. A blinded independent central review (BICR) was conducted, and the tumors were assessed after the first cycle and then every 8 weeks. After 15.5 months, the integrated analysis determined the overall response rate (ORR) was 57.4% (95% CI 43.2-70.8) and the median duration of response (DOR) was 10.4 months (95% CI 7.1-NR). Complete response rate was 7.4%. The median progression-free survival (PFS) was 11.2 months (95% CI 8.0-14.9) and median overall survival (OS) was 20.9 months (95% CI 14.9-NR).

In adults with solid tumors harboring an NTRK gene fusion or in ROS1-positive NSCLC the recommended dose is 600mg once daily. In pediatric patients, 12 years and older, the dose is based on body surface area. Entrectinib is available in 100mg and 200mg capsules which must be swallowed whole. Dosing adjustments are not recommended for patients with mild or moderate renal impairment (CrCl 30-90mL/min) and mild hepatic impairment (total bilirubin ≤1.5 times ULN). Patients with severe renal impairment and moderate or severe hepatic impairment have not been studied. Coadministration with moderate and strong CYP3A inhibitors should be avoided, but if unavoidable, dose adjustments are required. Administration with moderate and strong CYP3A inducers should be avoided. Entrectinib presented with a tolerable side effect profile as the integrated analysis of the three clinical trials reported most treatment-related adverse events being reversible with a dose reduction and of mild to moderate severity (Grade 1-2). Common side effects (>20%) of entrectinib treatment include: dysgeusia (44%), fatigue (48%), dizziness (38%), constipation (46%), nausea (34%), diarrhea (35%), dyspnea (30%), weight gain (25%), cognitive impairment (27%), cough...
tests due to risk of hepatotoxicity and serum uric acid levels due to observed hyperuricemia, is also recommended. 1,6

Similar to larotrectinib, entrectinib provides additional treatment options in patients with solid tumors with NTRK gene fusions who have progressed following previous treatment or have no alternative treatments available. It also adds to the armamentarium for treatment of metastatic ROS1 rearrangement positive NSCLC. Entrectinib’s tissue agonist-approval is a part of the shift in cancer treatments to target specific genetic features rather than tumor type, with encouraging results.

<table>
<thead>
<tr>
<th></th>
<th>Entrectinib (Rozlytrek) Approved August 2019</th>
<th>Larotrectinib (Vitrakvi) Approved November 2018</th>
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<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>600mg once daily</td>
<td>100mg twice daily</td>
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<tr>
<td><strong>Dosage Form(s)</strong></td>
<td>Capsules: 100mg, 200mg</td>
<td>Capsules: 25mg, 100mg Oral solution: 20mg/mL</td>
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<tr>
<td><strong>Renal Dose Adjustment(s)</strong></td>
<td>No dose adjustment is recommended for patients with mild or moderate renal impairment (CrCl 30 to &lt; 90 mL/min)</td>
<td>No dose adjustment is recommended for patients with renal impairment (any severity)</td>
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<tr>
<td><strong>Hepatic Dose Adjustment(s)</strong></td>
<td>No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin &lt;1.5 times ULN)</td>
<td>No dose adjust is recommended with mild hepatic impairment (Child-Pugh score A) Dose reduce in moderate or severe hepatic impairment (Child-Pugh score B and C)</td>
</tr>
<tr>
<td><strong>Drug Interaction(s)</strong></td>
<td>Dose reduce with moderate or strong 3A inhibitors and avoid with moderate or strong 3A inducers</td>
<td>Dose reduce with strong 3A4 inhibitors and increase dose with strong 3A4 inducers</td>
</tr>
</tbody>
</table>

References:

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7. Vitrakvi (larotrectinib) [prescribing information]. Stamford, CT: Loxo Oncology, Inc; November 2018
Nubeqa (darolutamide): A New Approach to Non-metastatic Castrate-resistant Prostate Cancer
Written by: Catherine Rothery, Pharm.D. Candidate 2020

Prostate cancer is the second leading cause of cancer-related deaths in American men. Despite having a 5-year relative survival rate of nearly 100% for localized and regional prostate cancer, the survival rate decreases to 30% once distant metastasis occurs. Therefore, preventing metastasis is a high priority in men with prostate cancer. The majority of men with advanced disease eventually become resistant to androgen deprivation therapy (ADT), the standard of care for regional or advanced disease. They are then considered “castrate-resistant” and additional hormone therapy is needed to control the cancer and prevent the development of metastasis. Commonly used hormonal therapies include second-generation androgen receptor inhibitors (antiandrogens), such as apalutamide and enzalutamide, in addition to ADT.

Although both apalutamide and enzalutamide have demonstrated a statistically significant benefit in metastasis-free survival, neither of these agents have demonstrated an overall survival (OS) benefit based on interim analyses of the phase 3 trials in nonmetastatic castrate-resistant prostate cancer (nmCRPC). It is important to note these data are not yet mature. In the SPARTAN study evaluating apalutamide versus placebo on metastasis-free survival in nmCRPC, median OS was not reached (NR) in the apalutamide group, compared to 39 months in the placebo group (HR 0.7; 95% CI 0.47-1.04; p = 0.07). Similarly, in the PROSPER study, which assessed enzalutamide versus placebo in men with nmCRPC, OS was NR in both groups (HR 0.8; 95% CI 0.58-1.09; p = 0.15). Both apalutamide and enzalutamide are also associated with significant toxicities, including seizures, thyroid dysfunction, QT prolongation, fractures, and posterior reversible encephalopathy syndrome. Darolutamide, the newest antiandrogen, is promising due to a potentially milder side effect profile and possible OS benefits.

The FDA approved darolutamide on July 30, 2019 for nmCRPC. The drug is dosed as 600 mg (two 300 mg tablets) by mouth twice daily with food, and dose adjustments are recommended for severe renal or moderate hepatic impairment. Exposure to darolutamide is impacted when P-glycoprotein (P-gp) inhibitors/inducers are used in combination with CYP3A4 inhibitors/inducers. In contrast with the other drugs in the antiandrogen class, the novel structure of this agent yields a lower blood-brain barrier penetration, which may reduce the severity of adverse effects. The most common adverse effects (~10%) of darolutamide are fatigue, neutropenia, increased serum aminotransferase and bilirubin, and asthenia. The darolutamide drug label contains a warning for embryo-fetal toxicity, so males should use contraception during and one week after treatment if they are with females of reproductive potential. The most recent study supporting the use of darolutamide in men with nmCRPC was a phase 3, multinational, randomized, double-blind, placebo-controlled trial known as the ARAMIS trial. The ARAMIS population consisted of 1509 men with nmCRPC and a prostate specific antigen (PSA) doubling time of 10 months or less. The subjects were given darolutamide (600 mg twice daily) or placebo in a 2:1 ratio, while continuing to receive ADT as either luteinizing hormone-releasing hormone (LH-RH) agonist or antagonist. The median age in both groups was 74 years, and the majority of patients had received two or more hormonal therapies. The primary outcome, median metastasis-free survival, was 40.4 months for darolutamide versus 18.4 months for placebo (HR 0.41; 95% CI 0.34-0.5; p = 0.001). The benefit in metastasis-free survival in this study was similar to the benefit seen with apalutamide and enzalutamide. Secondary outcomes, including OS and time to pain progression, also appeared to favor darolutamide over placebo (HR for death = 0.71; 95% CI 0.5-0.99; p = 0.045), though OS data are not mature at this time.

Adverse effect profiles were similar between treatment versus placebo groups, except for any grade fatigue being more common with darolutamide (12.1%) versus placebo (8.7%). Notably, the frequency of any grade fatigue was even higher for apalutamide (30.4%) versus placebo (21.1%) in the SPARTAN study and for enzalutamide (33%) versus placebo (14%) in the
The ARAMIS trial also had a smaller percentage of patients discontinue the trial regimen due to adverse events (darolutamide 8.9%; placebo 8.7%) compared to the SPARTAN trial (apalutamide 10.6%; placebo 7%), and had a similar discontinuation rate when compared to the PROSPER trial (enzalutamide 9%; placebo 6%). The incidence of more significant side effects associated with apalutamide and enzalutamide, such as seizures, fractures, and CNS-related effects, were low and similar in both the darolutamide and placebo groups. The adverse effect profile in the ARAMIS trial suggests darolutamide may be better tolerated than enzalutamide and apalutamide in patients with nmCRPC, though the lack of head-to-head studies make it difficult to determine which drug is superior. If the OS benefit seen during interim analysis holds in the final analysis, darolutamide may become the androgen of choice for nmCRPC in combination with ADT, due to its efficacy and favorable adverse effect profile.

References:
Losing Your Mind: Chemo-Brain

Written by: Logan Johnson, Pharm.D. Candidate 2022

Patients diagnosed with cancer have a long, trying road ahead of them. After treatment with radiation and/or chemotherapy, which is associated with numerous acute side effects, patients must also face the potential for long-term outcomes. Months to years after treatment patients can be affected by their cancer regimen sometimes in ways we cannot visibly see. One of these is neurological, often termed “chemo-brain” by patients and caregivers. Current treatments for cancer cause changes deep within the brain and its structure which alter the patient’s cognitive ability. Multiple studies have shown the diminishing effects on different areas of brain structure and brain function.

In the brain, dendritic spines line the hippocampus in thousands of synapses. These excitatory synapses are thought to be correlated with memory and learning processes. Being extremely sensitive to stress, the spines are easily transformed, as seen in many neurodegenerative diseases. When a patient receives chemotherapy, many of these dendritic spines are destroyed. This loss in excitatory synapses provides an explanation to the decline in hippocampal volume. In contrast to damage to dendritic spines by non-chemotherapy, such as head trauma, which can be reversed within minutes to hours, the damage by chemotherapy is irreversible. Early loss of memory after chemotherapy is explained by the decrease in synapses, but the later induced neurodegenerative diseases are results of the death of the neurons in the hippocampus that no longer receive excitatory signals due to complete destruction of the synapses.

While the synapses experience loss in number, the brain itself experiences loss in size. As brain matter plays the biggest role in human cognition, any decrease in size will negatively affect both brain function and memory. A study comparing children with acute lymphoblastic leukemia (ALL) receiving treatment with methotrexate and dexamethasone to a control group found at least some form of cognitive decline after chemotherapy. The children tested were between the ages of 4 and 16 years old, but they had to be 7 or older to participate in the imaging portion of the test. They completed the Wechsler Abbreviated Scale of Intelligence 2nd Edition (WASI-II) to estimate their level of intelligence. A visual test, the Rapid Visual Information Processing (RVP) subtest, was also conducted to determine their visual sustained attention along with the Reaction Time (RTI) subtest to measure visual information speed and ability to process. These tests were scheduled 3-4 months post-treatment of methotrexate and dexamethasone to ensure enough time was allotted to remove the drug from the patient’s system. In this study, children post-chemotherapy experienced lower information processing capacity, but no difference was found when testing the speed of processing compared to the control group.

In addition to the loss of synapses and reduction in brain size, chemotherapy may also shrink white matter and the neuronal web. This circuit of neurons is how information gets transported throughout the body and, essentially, how memories are stored. These changes do not appear initially when gray matter volume or physical surface area of the brain are measured. In a study observing patients with nasopharyngeal carcinoma after radiation therapy, gray matter volume and temporal lobe volumes decrease time-dependently, while ventricles increase in size through dilation. The MoCA (Beijing version) and was used to determine the general cognitive function of the patients before initiation of therapy and 3 months post-therapy. Patients undergoing this study were between the ages of 18 and 65 and had an initial MoCA score of 26 or greater. Using a specified cognitive assessment, the scores obtained from the test were negatively correlated with time following radiation therapy. This study revealed irradiation was linked to post-treatment loss of neurons and synapses. The magnitude of impairment of the brain depended on the extent of treatment, though all treatments did show some damage. A significant negative correlation (p-value equal to 0.0007) existed between the scores on the assessment test and dilation of the ventricles. Understanding the dose of radiation which limits damage to the brain is extremely important in patients due to the dose-dependent macrostructural decrease in volume after radiation therapy.
Chemotherapy and radiation are known to alter brain size and function, at times in a dose-dependent manner. Any amount of these toxic drugs is likely to have effects during and after treatment. Investigating these life-long neurologic adverse drug reactions is of utmost importance to patient quality of life. This provides the framework for opportunities in future research to mitigate the impact of “chemo-brain.”

References:
