LifeSci Capital KOL Series – Novel Approaches for the Treatment of RASopathies

We recently attended a Key Opinion Leader event focused on novel approaches for the diagnosis and treatment of RASopathies and juvenile myelomonocytic leukemia (JMML) as complication of RAS associated germline mutations. The event featured a presentation from Doctors Eliot Stiegllitz and Bruce Gelb. Dr. Stiegllitz is an assistant professor at the University of California San Francisco in the division of pediatric hematology and oncology. Dr. Gelb is the director and Gogel family professor, of the Mindich child health and development institute at the Ichan School of Medicine at Mount Sinai. In addition, event sponsor Onconova Therapeutics (NasdaqCM: ONTX) provided an update of its ongoing myelodysplastic syndromes (MDS) program using rigosertib, a small molecule that acts as a RAS mimetic to inhibit cellular signaling. A replay of the event is available here. Onconova, recently announced that it established a research and clinical collaboration with the National Cancer Institute (NCI) for the evaluation of rigosertib in pediatric RASopathies.

Germline Mutations in RAS and Associated Syndromes. RASopathies are a class of developmental disorders, which are characterized by germline mutations in genes encoding RAS, or components of the RAS signaling pathway. The majority of these disorders are autosomal dominant, meaning that a mutation in just one copy of the gene may lead to the manifestation of the disease. RASopathies share various phenotypic and clinical features including craniofacial dysmorphology, cardiac defects, musculoskeletal abnormalities, developmental delay, and an increased risk of developing cancer. A series of elegant genetic studies helped elucidate a set of genes that are linked to these RAS driven disorders, and are depicted in Figure 1. The left side of the figure depicts the RAS pathway and the genes that are linked to each syndrome. The right side of the figure tabulates the phenotype-genotype relationships of the different syndromes. The event highlighted Noonan Syndrome (NS), which is the most common of these disorders, and Juvenile myelomonocytic leukemia (JMML), a hematological malignancy that is associated with several RASopathies.

Figure 1. Genotype – Phenotype Relationships of RASopathies

Unmet Clinical Need in JMML. Juvenile myelomonocytic leukemia (JMML) is a hematological disorder of early childhood that is characterized by the over proliferation of monocytes, which infiltrate various solid organs including the spleen, liver, and lungs. JMML accounts for approximately 2.5% of childhood leukemia cases, and according to Dr. Stiegllitz, is one of the purest forms of RAS driven malignancy. The majority of patients with JMML harbor mutually exclusive mutations in 1 out of the 5 following genes: PPTN11 (SHP-2), NRAS, KRAS, NF-1 or CBL. Hematopoietic stem cell transplantation is a curative option for these patients, however 50% of those receiving a transplant will eventually relapse, highlighting the unmet need for improved treatments.

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MEK inhibition Nominated as Potential Treatment Option for JMML. Targeting the RAS protein itself has been historically difficult. As a way to circumvent RAS and better address JMML patients, Dr. Stieglitz and his colleagues have proposed to indirectly target RAS by inhibiting MEK activity, a protein kinase downstream of RAS. The group recently launched a Phase II study evaluating Novartis’ (NYSE: NVS) MEK inhibitor, Mekinist (trametinib) in children with relapsed or refractory JMML.

Dr. Stieglitz also described the design of a proposed international clinical trial. The purpose of this prospective study is to examine the efficacy of MEK inhibition as a monotherapy or in combination the azacitidine in patients that have been stratified using mutational and methylation status. Figure 2 depicts the proposed trial design. JMML patients with an available stem cell donor will be genotyped and their methylation status will be assessed prior to enrollment. Those with one alteration in the RAS pathway and low levels of methylation will receive 2-3 cycles of MEK inhibitor monotherapy. Patients with either more than one mutation in the RAS signaling pathway or high levels of methylation will receive 2-3 cycles of a MEK inhibitor plus azacitidine, and will be evaluated for possible stem cell transplantation at the end of the study. Durable responses are imperative in these children given the 20% survival rate after receiving a stem cell transplant. In Dr. Stieglitz’s opinion, the stratification of patients based on their underlying genetic and epigenetic profile may offer a framework for treating JMML patients in the future, and could ultimately streamline these children into the appropriate clinical trials once they relapse.

Figure 2. Proposed Risk Stratification Study

![Diagram of proposed trial design](source: KOL Presentation)

Genetic Characterization of JMML Suggests Actionable Targets. Understanding the underlying genetic and epigenetic profile of JMML patients may help to identify appropriate treatment options. Work performed by Dr. Stieglitz and his colleagues has helped elucidate the mutational landscape of the disease and provided actionable targets with therapeutic implications. Of note, work done by this group found that 14% of JMMLs harbor mutations in epigenetic modifier genes, such as ASXL and DNMT3A. Alterations in these genes were often associated with widespread hypermethylation, suggesting that patients with these alterations may be candidates for treatment with DNA hypomethylating agents (HMA). This is important since there is preclinical and clinical data suggesting that the combination of epigenetic therapy and inhibition of signaling derived from RAS may be an effective strategy to limit hematological malignancies such as leukemia and MDS.

Work by Dr. Stieglitz and his colleagues also found a close association between monosomy 7 and alterations in EZH2, a methyltransferase involved in histone methylation. In fact, all of the profiled patients with mutations in EZH2 also had monosomy 7,
which is a partial deletion of chromosome 7. Of note, a Phase III study using Onconova's rigosertib in MDS demonstrated that the drug was particularly effective in patients with monosomy 7. The median overall survival (mOS) in this group was 5.6 months (n=16), compared to 2.8 months (n=13) in patients treated with best standard of care (HR= 0.24; p= 0.003). Together, these observations highlight the potential of using mutation-based stratification as a way to identify patients that could benefit from a specific therapy.

- **A Personalized Drug Screen Identified Rigosertib as a Potential Treatment Option in JMML.** Dr. Stieglitz presented data, shown in Figure 3, describing a potential role for rigosertib in JMML. The results are from an automated, individualized drug screen performed on one JMML patient with a KRAS mutation. 100 drugs were separately tested in cultured blasts collected from the patient. As shown in the graph, rigosertib, highlighted within the red box, was very effective at limiting the viability of blasts 72 hours after treatment compared to the other tested compounds.

  **Figure 3. Results from a Drug Screen of JMML Patient**

- **RAS Pathway is an Attractive Target for Treatment of Hypertrophic Cardiomyopathy.** The event highlighted the role Noonan syndrome (NS) in the development of hypertrophic cardiomyopathy (HCM). Work done by Dr. Gelb's group identified PTPN11 (SHP2) as one of the genes responsible for NS, which affects 1 in 1,000-2,500 live births. Apart from SHP2, NS is linked to various genes, outlined in Figure 1. Dr. Gelb suggested that HCM may benefit from therapies targeting RAS signaling. HCM is the leading cause of sudden death in children and young adults. The disease is characterized by enlarged heart muscles that cause the walls of the ventricles to thicken, and can ultimately result in heart failure and death. Dr. Gelb featured a natural history study showing a dismal survival rate in NS patients that presented with heart failure at less than 6 months of age. There is currently no approved therapy for these children.

  HCM is almost always present in patients with germline alterations in RAF1, a protein kinase in the RAS/MAPK pathway. Dr. Gelb presented a preclinical study in HCM, where treatment with a MEK inhibitor was able to rescue cardiac function postnatally. He mentioned that he knew of three cases where pediatric patients with HCM are currently being treated off-label with trametinib, and he expected to see proof of principle with the drug. However, Dr. Gelb did raise concerns regarding the safety profile of trametinib, as patients treated with drug often experience rash, diarrhea, and severe leukopenia. He suggested that any drug in development for these patients would have to have a clean safety profile in order to be of use in this particular population. He acknowledged that
the data so far with rigosertib were encouraging, and he looked forward to reviewing the safety profile from its use in JMML as an indicator of its potential for HCM.

- **Onconova Plans to Address JMML with Rigosertib.** Onconova recently announced intentions to address pediatric patients with RASopathies that are complicated by the development of RAS associated malignancies such as JMML. The Company established a collaboration with the National Cancer Institute (NCI) and is planning a broad clinical trial for pediatric patients with RASopathies. As proof of concept, Dr. Steven Fruchtman, The Company’s chief medical officer, presented preclinical data showing a dose dependent cytotoxic effect of rigosertib in an *in vitro* model of malignant peripheral nerve sheath tumors (MPNSTs). These cells harbor loss of function mutations in *NF1*, a gene involved in the regulation of RAS signaling.

Aside from the proposed development of rigosertib in JMML, Onconova is currently evaluating the treatment in multiple randomized studies. One of the most notable is the **Phase III INSPIRE** study evaluating IV-rigosertib for MDS. The study is expected to enroll about 225 patients with high risk (HR)-MDS who are refractory to prior hypomethylating agents. Patients are being randomized 2:1 to IV rigosertib and best supportive care (BSC), or physician’s choice of treatment plus BSC. An interim analysis from this study is expected during the fourth quarter of 2017. In addition, Onconova is conducting an extended portion of a **Phase II** study using oral rigosertib and azacitidine in 40 patients as a first-line treatment option for HR-MDS.

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