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Sector Analysis Update:
Rare Diseases/Neuro-oncology Companies at ASCO

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Last week saw the conclusion of the American Society of Clinical Oncology (ASCO) annual meeting, and the winding down of other principal academic meetings favored by companies in our biotech universes. Seasonally, biotech shares tend to trade up ahead of ASCO and this year has followed the typical pattern. The NASDAQ Biotech Index (NBI) climbed 15% into the event, but even with that gain, the sector lags the S&P 500: +3% vs -20%+ year-to-date. From this point forward, as noted in an recent analysis conducted by Jefferies (Biotechnology: A Macro View; US Equity Research, June 2016), general seasonal strength in the biotech sector peaks at or shortly after ASCO, as investors move from an index play to focus their attention on specific company opportunities. This move, from general sector to company-specific investment focus, is particularly forceful this year, as evidenced by the disparate performance of selected companies from our Neuro-oncology sector, which we discuss further in this update.

This year’s ASCO continued the trend seen in other cancer-related academic meetings from earlier in 2016, with a strong showing by a variety of clinical studies employing combination therapy approaches, some with results surprising to clinicians, while other ASCO highlights centered on the use of molecular diagnostics to better stratify patients or target therapies. One study, the ongoing MyPathway PIIa “umbrella basket” trial being conducted by Genentech, reported interim data on the first 129 patients of the 500 patient trial and was particularly noteworthy as being one of the first to target treatments to specific tumor genetic mutations rather than treat based on cancer type. This and other such trials are leading what may be a paradigm shift in cancer treatment—from that based upon on cancer subtype – i.e., lung or pancreatic or stomach cancer -- to that based on specific genetic alterations in molecular pathways, such EFGR, BRAF, hedgehog and others, regardless of cancer (organ) subtype.

In another news-making and ASCO-featured clinical study, Guardant Health Inc. released data from one of the largest genomic analysis studies conducted to date that included genetic information from 15,191 patients across 50 (primarily solid) tumor types using their proprietary liquid biopsy (circulating tumor DNA) test, Guardant360. Among its findings, two-thirds of the results from ctDNA blood tests involved mutations that could be targeted and treated with currently available drugs. More interestingly, however, was the finding that the test discovered novel genomic alterations which were associated with cancer drug resistance. The value of such information, being able to analyze in real-time the genomic progression of cancer in a non-invasive manner, has the potential to drive cancer treatment away from the single agent, monotherapy approach and towards a proactive multi-disciplinary approach that changes treatment strategy in response to tumor genomic progression. Further, among other significant study results was evidence a high level of clinical utility,
particularly for lung cancer, where tissue-based biopsy information in the test population, was found insufficient to make treatment decisions in as much as 63% of participating patients.

Regardless of the Guardant 360 study, based upon numerous ASCO reported clinical studies, the concept of employing multidisciplinary approaches clearly is becoming mainstream, especially in treating difficult cancers such as melanoma, certain lung cancers and brain cancers. From Plenary sessions featuring such combination studies, there appeared to be consensus enthusiasm in two areas related particularly to brain cancer: the use of tandem (two) stem cell transplants in combination with immunotherapy for treating children with neuroblastoma and the use of temozolomide concurrently with and post radiation in glioblastoma (GBM) patients over the age of 65—a patient set for which there has not been any standard of care and practice varies widely around the world.

Trial data from both ends of the age spectrum produced results that surprised researchers and clinicians. Doctors have been searching for alternative treatments for pediatric neuroblastoma as the currently used regimens in treating these high risk patients are the most aggressive and toxic radio/chemotherapy used for children with cancer. In an ASCO Plenary session reporting the outcome of a Phase III 2nd (tandem) autologous stem cell treatment trial funded by the NCI, results showed a significant improvement at 3 years post treatment, whereby 61.4% of pediatric patients were alive and cancer-free compared to only 48.4% receiving a single stem cell treatment. The overall survival (OS) rate was enhanced further to 85.5% at 3 years when immunotherapy was added. The surprise at the other end of the age spectrum, patients with glioblastoma who are over 65 years old, came in another Plenary session presentation that indicated a significant survival benefit of adding temozolomide to a shortened (3-4 weeks) course of radiation, rather than the long course (6-9 weeks) of radiation monotherapy which is typically administered. Patients over the age of 65 represent about 50% of GBM patients. The randomized 562 patient Phase III study showed that the combination treatment improved the overall median survival time to 9.3 months and increased progression-free survival to 5.3 months from 3.9 months. One year survival rate increased from 22.2% to 37.8%. The median patient age was 73 years. The major surprise however, was that patients benefitted from the combination treatment regardless of whether they had a methylated or unmethylated MGMT promoter status.

The following are some ASCO highlights from companies in our Rare Disease/Neuro-Oncology sector:

**VBL, Therapeutics** (VBLT-$4.00/Not rated): In addition to presentation of Phase1/2a clinical results in recurrent platinum-resistant ovarian cancer, VBL presented new data from a retrospective pooled meta-analysis of published Phase II clinical study outcomes using Avastin® (bevacizumab) as a monotherapy that was compared to the Phase II results of VB-111, VBL’s gene-based therapeutic. In a 46 patient study, individuals were treated with VB-111, and upon progression, re-treated with Avastin alone in a “limited exposure” cohort, or with the combination of Avastin + VB-111 in a continuous exposure cohort. The pooled Avastin data was derived from 8 studies in recurrent GBM and were published between 2005 and 2015.

VBL’s analysis showed that adding VBL-111 to Avastin in a continuous exposure protocol significantly improved overall survival. Compared to the pooled data, patients in an VB-111 continuous exposure setting had superior overall survival, 59 weeks compared to 32 weeks (p=0.0295, log-rank test) with a Hazard Ratio of 0.62 (95% CI: 0.40-0.96). Most interesting was the finding that patients who “spiked” a fever at least once after VB-111 administration experienced a enhanced overall survival...
benefit of 64 weeks compared to 34 weeks in patients who did not experience a fever (p=0.03). We have observed that some other immunotherapy based studies have also noted a “fever effect”, which is hypothesized to indicate a much more aggressive immune response. This data supports the premise behind VBL’s currently on-going Phase III GLOBE trial (VBL-111 + Avastin). The company expects to report an event-driven interim analysis, timing depending upon enrollment and event occurrence, sometime during the first half of 2017. VBL completed a $24 million registered direct on June 16th to continue to fund its clinical trial programs. Despite recent volatility, the stock remains in an uptrend as long as it stays above 3.75

**ImmunoCellular Therapeutics, Ltd.** (IMUC/$0.22/Not rated): IMUC announced at ASCO that the first patient in its Phase III registration trial for ICT-107 in newly diagnosed GBM had been treated. ICT-107 is a patient-specific dendritic cell-based immunotherapy targeting multiple tumor-associated antigens on glioblastoma cells. IMUC has received agreement with the FDA on a Special Protocol Assessment (SPA) relative to primary and secondary trial endpoints and the statistical plan for the trial. IMUC has also received $19.9 million for the California Institute for Regenerative Medicine (CIRM) in financial support for the trial. The Phase III trial is a 120 international (US +9 countries) site trial seeking to enroll 414 HLA-A2-positive patients. To support timely enrollment, IMUC has established agreements with the European Organization for Research and Treatment of Cancer (EORTC), the Alliance for Clinical Trials in Oncology in the US, and the Canadian Brain Tumor Consortium. The primary endpoint is overall survival with secondary endpoints of progression-free survival and safety as well as survival in two pre-specified MGMT subgroups.

**Tracon Pharmaceuticals, Inc.** (TCON/$4.59/Not rated): Tracon presented data on several of its clinical programs which combine its novel antibody-like small molecules with Avastin (bevacizumab) standard of care (SOC). TRC105 is a novel, clinical stage antibody to endoglin, a protein that mediates anti-VEGF escape through overexpression of factors promoting proliferating endothelial cells that in turn promote tumor angiogenesis, the process of new blood vessel formation and a key driver of tumor growth. TRC105 is currently being studied in multiple Phase 2 clinical trials sponsored by TRACON or the National Cancer Institute for the treatment of solid tumor types, in combination with VEGF inhibitors. In the small compassionate use study using the Tracon’s TRC105 endoglin antibody therapy for choriocarcinoma, an aggressive form of one of several rare gestational trophoblastic diseases (GTD) that develops in the placenta of young women who (primarily) have had miscarriages, abortions or tubal pregnancies, an ongoing complete response was observed in one of the two patients treated. This CR event provided the support for TCON to plan on initiating a global Phase II trial in choriocarcinoma in the second half of 2016.

Tracon also presented a poster, “A Phase II trial of TRC105 for bevacizumab (Avastin) refractory glioblastoma”. This was an open label Phase II trial for patients who progressed on Avastin. Because TRC105 does not seem to have much independent efficacy as a monotherapy, the study was designed to evaluate the synergy in a combination therapy. The study population
was split into a monotherapy arm (6 patients) and combination arm (22 patients), with the primary endpoint of overall survival that would exceed the historic Avastin OS of 4.0 months. The patients who received the combination therapy achieved an OS of 5.75 months whereas the monotherapy patients had progressed by 1.4 months. TRC105 is currently in a randomized Phase II trial in combination with Avastin for GBM in Avastin naïve patients. Results of this trial are expected late 2016 or early 2017.

Tocagen (private) reported a retrospective overall survival and safety analysis of Phase I results of its Toca 511/Toca FC GBM regimen compared to a lomustine (CCNU) control in subjects with GBM in a 1st or 2nd recurrence. Toca 511 is a retrovirus designed to spread selectively in cancer cells, carrying a gene to activate the second part of the therapy, an investigational formulation of 5-FC called Toca FC. Within Toca 511 transfected cancer cells, the gene produces an enzyme which converts 5-FC into the anti-cancer drug 5-FU. This in situ drug activation by a gene strategy is conceptually similar to that being explored by Ziopharm Oncology Inc. (ZIOP/$5.73/Not rated). The pooled Phase I data showed highly significant improvement in OS (HR = 0.48), p < 0.001 with similar effect in the setting of surgical resection (OS HR 0.45, p = 0.003) and nonsurgical resection with a biopsy needle (OS HR 0.56, p = 0.060). Fewer related Grade ≥ 3 adverse events (AEs) were reported for Toca 511/Toca FC (2.5%) vs. lomustine (36.9%). There was a virtual absence of hematologic toxicity for Toca 511/Toca FC vs. lomustine (Grade ≥ 3 thrombocytopenia 23.8%). Discontinuations for AEs occurred in 0% for Toca 511/Toca FC vs. 4.8% for lomustine. Toca 511/Toca FC is currently in a Phase II/III 170 patient registration trial. The unique approach of Toca 511/Toca FC coupled with the fact that treatment is not Avastin dependent makes the product highly differentiated from competitors. With a demonstrated improved safety profile compared to SOC treatments, Toca 511/Toca 5F could represent a break-through in GBM treatment if efficacy continues to be substantiated in the registration trial.

CellDex Inc. (CLDX/$4.25/Not rated): Although CellDex made the decision to suspend clinical development of its GBM candidate last March, the Company has continued to develop other immunotherapy products in other indications. In a Phase II multi-center, randomized combination study for high risk melanoma reported at ASCO, CellDex announced that the combination of CDX-1401, an IgG-1 antibody fusion protein to enhance immune response, and pre-treatment with CDX-301, a hematopoietic cytokine that drives dendritic cell and hematopoietic stem cell (HSCs) cell expansion, resulted in an enhanced innate immune cell responses. The study which randomized 60 patients with resected stage IIb through IV melanoma into two cohorts (n=30 each). The pre-treatment cohort received two cycles of CDX-301 prior to CDX-1401 to assess whether the immune response to the NY-ESO-1 tumor-associated protein elicited by CDX-1401 could be substantially increased together with the expansion of dendritic cells populations, which are key in generating immune responses. The CDX-301 pre-treatment arm results were compared to a second cohort, who did not receive CDX-301 pretreatment. NY-ESO-1 specific T cell responses, the target of CDX-1401, were significantly greater and developed earlier in Cohort 1 compared to Cohort 2. In addition, all patients in Cohort 1 (n=30) achieved a specific NY-ESO-1-specific T cell response compared to only 22 out of 30 patients in Cohort 2. Substantial increases in innate immune cells (dendritic cells, natural killer cells and monocytes) and greater increases in antibody titer were observed in the CDX-301 pre-treated Cohort 1. Although the stock has since retreated, CellDex shares had moved up off of May lows in advance of the ASCO data and appear to now be in a base-building phase.
Closing Thought: From a general perspective, the move towards combination therapies that began to emerge last year has been fully embraced by practitioners, as evidenced by the high proportion of data being released around adding novel treatments to standard of care. Treatment goals are also shifting and moving away from the traditional focus on primary disease to obtaining a far better understanding of individual disease progression dynamics and its impact on the prevention or management of metastasis. The insights from emerging molecular diagnostic technologies that allow real-time non-invasive “tracking” of the genomic progression of tumors is going to revolutionize treatment strategy and drive the use of multiple treatment approaches (chemo/immune/checkpoint inhibitors, etc.) within individual patients over the time course of their disease. This paradigm shift, from “mono” to many treatment strategies for individual patients, could have a significant future impact for emerging biotechs in the cancer space. It could become harder to differentiate products and harder for individual drugs to reach the “used by all” block-buster status achieved by Taxol, doxorubicin, and others 15 or 20 years ago for instance, as cancer treatment moves towards highly personalized medicine. SG

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- **Regulatory risks** – the companies in the DJ CNS Rare Disease Sector are subject to regulatory review for their ongoing research and development activities and manufacturing operations with local, state and federal governmental agencies both in the US and Internationally.

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- **Historical lack of profitability** – To date this year and in past years, most of the companies in the DJ CNS Rare Disease Sector have not operated on a profitable basis, and are not forecast to do so in the immediate future. Although companies typically have been able to raise funds from the capital markets, there can be no guarantee that any particular company will not be able raise additional operating capital in the future should losses continue.

- **Competitive Markets** – This universe of companies operate in a highly competitive marketplace, where speed to market, clinical results and other factors bear on a company’s viability. There can be no assurance that any one company will be able to continue to market or later launch its products successfully in these competitive markets in the future.

Note: All charts courtesy of Stockcharts.com

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