We attended the 2017 American Society of Clinical Oncology (ASCO) meeting from June 2nd to June 6th, 2017 and met with researchers, collaborators, and clinical investigators who presented preclinical and clinical data from our covered companies and those of interest. This is our first note from this series. Relevant presentations in this note affect Tracon Pharma (NasdaqGM: TCON), Mirati Therapeutics (NasdaqCM: MRTX), Medicinova (NasdaqGM: MNOV), Basilea Pharmaceutica (SWX: BSLN.SW), Rexahn Pharmaceuticals (NYSEMKT: RNN), Onconova Therapeutics (NasdaqGM: ONTX), and Transgene (EPA: TNG.PA).

- **Tracon Pharma (NasdaqGM: TCON)**
  - Phase III TAPPAS study with TRC105 plus Votrient (pazopanib) for angiosarcoma ongoing.
  - Correlation observed between TRC105 administration and circulating endoglin, indicating that the drug is engaging its target.
  - Partial responses seen in refractory solid tumors combining TRC102 with temozolomide.

**Poster: Biomarker modulation in patients treated with TRC105 in combination with anti-VEGF therapy.**

This poster detailed biomarker studies from Phase II trials using TRC105, an anti-endoglin antibody, in combination with anti-VEGF therapy. Plasma samples were collected from 18 patients with metastatic renal cell carcinoma (mRCC), 18 patients with advanced soft tissue sarcoma, and 22 patients with glioblastoma multiforme (GBM). Baseline and on-treatment changes in 22 soluble protein biomarkers were assessed using Aushon BioSystems CiraScan protein multiplex arrays. Following treatment with TRC105, there were noticeable increases in soluble endoglin levels from baseline across all three patient populations, indicating that TRC105 is actively engaging its target on the tumor and inducing cell death. Interestingly, the sarcoma and GBM studies had a lead-in phase with VEGF monotherapy, and so the poster showed that endoglin increases are dependent on TRC105 administration, and not VEGF inhibition.

For sarcoma and mRCC patients, baseline markers were analyzed to help predict which patients respond to treatment. It was found that lower baseline expression of soluble osteopontin (OPN) (p= 0.0264) and higher baseline expression of soluble transforming growth factor-β receptor III (TGFBR3) (p= 0.0028) were associated with responses in mRCC. These biomarkers are being further investigated in the ongoing Phase II TRAXAR study using TRC105 and Pfizer’s (NYSE: PFE) Inlyta (axitinib). Lower baseline expression of soluble intracellular adhesion molecule-1 (ICAM-1) (p= 0.018) and thrombospondin-2 (TSP-2) (p= 0.041) were associated with responses in sarcoma patients, and these markers are being examined as part of the Phase II study combining TRC105 with Novartis’s (NYSE: NVS) Votrient (pazopanib) in soft tissue sarcoma, and the Phase III TAPPAS trial in angiosarcoma.

**Poster: Tappas: An adaptive enrichment phase 3 trial of TRC105 and pazopanib versus pazopanib alone in patients with advanced angiosarcoma (AAS)**

Tracon is currently conducting the Phase III TAPPAS study combining its endoglin targeting antibody, TRC105 with Votrient for patients with angiosarcoma. This poster discussed the design of the study, which has recently won the Most Innovative Clinical Trial Design award at the 2017 Clinical and Research Excellence (CARE) awards. There are currently no drugs approved specifically for angiosarcoma, which is a rare form of soft tissue sarcoma. Tracon's study is the first Phase III study focused on this indication.

124 patients in the US and EU with advanced angiosarcoma will be randomized 1:1 to receive 10 mg/kg/week of TRC105 plus 600 - 800 mg/day of Votrient or 600 - 800 mg/day Votrient monotherapy. Patients are being stratified based on cutaneous and non-cutaneous subtype, and the number of prior chemotherapies. Cutaneous and visceral disease each make up roughly half of the angiosarcoma population. This study has an adaptive design, which will allow the Company to shift enrollment to up to 200 patients. The primary endpoint is median progression free survival (PFS), and secondary endpoints include overall response rate (ORR), overall survival (OS), and safety. Exploratory endpoints will examine the correlation between efficacy endpoints and endoglin expression on angiosarcoma tumor samples, circulating angiogenic protein biomarkers, and the number of endoglin expressing circulating tumor cells. As a reference, 9 patients with
angiosarcoma have been treated with the combination of TRC105 and *Votrient*, and complete responses were seen in 2 patients with cutaneous angiosarcoma. An interim data readout from this trial is expected in mid-2018, with full data coming in early 2019.

**Poster: Phase I trial of TRC102 (methoxyamine HCL) with Temozolomide (TMZ) in Patients with Solid Tumors and Lymphomas**

Tracon presented data from its Phase I study using TRC102 combined with temozolomide (TMZ) in patients with refractory solid tumors and lymphomas. TRC102 is a small molecule, base-excision repair (BER) inhibitor. BER is known to cause resistance to both alkylating agents and antimetabolite chemotherapy. This was a dose escalation trial that evaluated doses between 25 mg and 150 mg of TRC102 in combination with TMZ. The recommended Phase II dose (RP2D) was determined to be 125 mg of TRC102 in combination with 150 mg/m² of TMZ. Both of these agents are being dosed for 5 consecutive days in 28-day cycles. After the RP2D was determined, 15 additional patients were enrolled into an expansion cohort of lung, ovarian, or colorectal cancer. In total, 52 patients with the following types of cancer were enrolled in the study:

- Colon (n=14)
- Ovary (n= 6)
- Liver (n = 4)
- Breast (n= 3)
- Miscellaneous tumors (n= 25)

In total, 4 patients achieved a partial response (PR) to therapy, and 13 had stable disease. Responses occurred in KRAS positive colorectal cancer, ovarian cancer, and NSCLC. Notably, 3 of the PRs are ongoing for more than 30 weeks. In terms of safety, the side effect profile was considered manageable at the RP2D, and the dose limiting toxicity was anemia. An additional analysis was conducted in 5 colon cancer patients to determine DNA damage response (DDR) markers based on pre and post treatment biopsies. DDR responses were shown in 4 of the 5 patients, indicating that the combination treatment is inducing DNA damage. A Phase II study is ongoing evaluating TRC102 as a treatment for colon cancer, NSCLC, and granulosa cell ovarian cancer (GCOV).

- **Mirati Therapeutics (NasdaqCM: MRTX)**
  - Ongoing Phase II study with sitravatinib for well-differentiated/dedifferentiated (WD/DD) liposarcoma (LPS).
  - Preclinical data showed that treatment with sitravatinib inhibited tumor growth in WD/DD LPS.

**Poster: Phase 2 trial of the novel multi-receptor tyrosine kinase inhibitor sitravatinib in well-differentiated/ dedifferentiated liposarcoma**

This poster discussed the Phase II trial design using Mirati’s sitravatinib for patients with advanced well-differentiated/dedifferentiated (WD/DD) liposarcoma (LPS). Sitravatinib is a small molecule that targets a range of receptor tyrosine kinases (RTKs), including MET, PDGFRα/b, VEGFR, Axl, KIT, RET, FLT3, and others. The rationale for this trial is based on preclinical studies showing that phosphorylated IGF1-R, MET and PDGFRβ are highly expressed in WD/DD LPS cell lines, and that treatment with sitravatinib inhibited tumor growth. This is a single arm, open-label Simon 2-stage study. The first stage is planned to enroll 13 patients with WD/DD LPS who have measurable disease and have received 1 or more prior lines of systemic therapy, and evidence of progression in the prior 12 weeks. Each participant will receive 150 mg of daily oral sitravatinib for 21-day cycles.

If 2 or fewer patients achieve a 12-week PFS, then the study will not progress to the Phase II portion for LPS, and instead will enroll 4 patients each with malignant peripheral nerve sheath tumor (MPNST), synovial sarcoma, alveolar rhabdomyosarcoma, and alveolar soft part sarcoma (ASPS) to help guide additional Phase II study decisions. If 3 or more patients achieve a 12-week PFS, then the study will move on to the second portion, which will enroll 16 additional patients. If 8 or fewer of the 29 enrolled patients achieve a 12-week PFS, then the Company will not consider sitravatinib a promising agent for LPS. If 9 or more patients achieve a 12-week PFS, then additional development for LPS would be warranted. The primary endpoint of 12-week PFS endpoint is based on historical data. Secondary objectives include safety, ORR, and PFS. In addition, Mirati intends to use a reverse phase protein array to evaluate changes in total and phosphorylated RTK expression in baseline and mid-treatment tumor biopsies to assess activated RTKs in the tumor tissue.
confirm on-target drug activity, and evaluate potential signs of resistance. The Company will also use next generation sequencing to evaluate archival tumor tissue from patients to determine a defined set of potential RTK genetic alterations.

- Medicinova (NasdaqGM: MNOV)
  - Combination of ibudilast and TMZ in GBM had additive effect preclinically.
  - Clinical study being planned to assess ibudilast and TMZ for recurrent GBM.

Poster: Effect of treating glioblastoma with a cytokine inhibitor, ibudilast, in combination with temozolomide on survival in a patient-derived xenograft model.

Medicinova presented preclinical data using its orally administered small molecule MN-166 (ibudilast), a phosphodiesterase inhibitor (PDEI) with anti-inflammatory and neuroprotective properties, for the treatment for GBM. The standard of care for first-line GBM is surgical resection followed by temozolomide (TMZ) and radiation. This treatment in particular has benefited patients who have a methylated-MGMT promoter, although almost all patients will eventually progress. The presented study identified an increased expression of macrophage inhibitory factor (MIF) and its receptor CD74 in 168 GBM patient-derived tumor tissue samples. MIF is an inflammatory cytokine that ibudilast inhibits, and is hypothesized to be secreted from cancer stem cells. Notably, the co-expression of MIF and CD-74 were identified in 57% of the tissue samples, and statistically correlated with a shorter survival (p= 0.007).

The combination of 5 mg/kg or 20 mg/kg of oral ibudilast and 10 mg/kg of TMZ were compared to control in a PDX model. This model entailed MGMT unmethylated RN1 cells that were intracranially implanted into the brains of BALB/c nude mice. As shown in Figure 1, treatment with the combination led to an increase in median survival compared to control (114 days vs. 100.5 days; p=0.005). The median OS for mice treated with TMZ alone was 105.5 days. siRNA knockdown of MIF reduced tumor cell proliferation and increased sensitivity to TMZ preclinically, providing rationale for this combination to be investigated. A Phase IIa clinical study is being planned to evaluate the combination of ibudilast and TMZ for patients with recurrent Grade IV GBM.

Figure 1. Survival of Combination Treatment vs. Control

Survival proportions: Survival of Control Vs Combo

Basilea Pharmaceutica (SWX: BSLN.SW)

- Once daily oral BAL101553 shows similar PK profile to 2 hrs. IV BAL101553, without vascular toxicity.
- Patients treated with oral BAL101553 showed stable disease as best objective response.

**Poster 1**: A phase I study to assess the safety, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activities of BAL101553, a novel tumor checkpoint controller (TCC), administered as 48-hour infusion in adult patients with advanced solid tumors.

**Poster 2**: A phase I study to assess the safety, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activities of daily oral BAL101553, a novel tumor checkpoint controller (TCC) in adult patients with progressive or recurrent glioblastoma (GBM) or high-grade glioma.

**Poster 3**: Phase 1/2a trial of daily oral BAL101553, a novel tumor checkpoint controller (TCC), in advanced solid tumors.

Basilea Pharmaceutica presented three posters describing data from ongoing clinical trials with BAL101553, a vascular disrupting agent, in patients with advanced solid tumors, progressive glioblastoma and high-grade glioma. Recall the Company completed a Phase I/IIa trial with an intravenous formulation of BAL101553, showing evidence that vascular toxicity was related to the peak concentration of drug after one cycle of treatment. A daily oral formulation of this compound is currently being evaluated in Phase I/IIa trials discussed below, and previous data has shown that the formulation can be given daily to maintain drug levels over a sustained period.

The first poster reported data from an ongoing Phase I/IIa trial in adults with solid tumors, glioblastoma, or high-grade glioma. Interim data from this study indicated that oral BAL101553 was well tolerated, with no clinically relevant AEs at the 8-20 mg/kg treatment dose. The trial explored whether once daily oral BAL101553 reduced the peak concentration of drug required to maintain efficacy while sparing vascular toxicity. Previous preclinical findings showed enhanced efficacy of BAL101553 over TMZ in a xenograft mouse model of TMZ refractory GBM. Investigators found that daily oral administration of 16 mg was able to achieve a peak concentration similar to weekly administration of 60 mg/m² IV BAL101553, with no effects on blood pressure or vascular toxicity. Response to therapy was measured in a total of 19 patients receiving 2 cycles of oral BAL101553 either at ≤8 mg/kg or ≥16 mg/kg. Sixty percent (6/10) of patients treated with doses ≥16 mg/kg showed a best objective response of stable disease, compared to 22% (2/9) stable disease in patients treated with doses ≤ 8 mg/kg. These data suggest the once daily oral dose of BAL101553 is well tolerated, and that its activity is dose-dependent.

Basilea also gave an update on a Phase I trial that is assessing the safety and efficacy of IV BAL101553 in patients with advanced solid tumors. The study aims to extend the time of IV infusion of BAL101553 from 2 hours to 48 hours. The treatment scheme also includes administration of oral BAL101553 in place of IV infusion during the second treatment cycle. The proposed dosing strategy is intended to increase the concentration of drug in the blood. Figure 2 shows the current status of the Phase I/II and Phase I studies. The company expects full enrollment of the Phase I/IIa study of oral BAL101553 in patients with advanced solid tumor by the end of 2017.

**Figure 2. Progress of Studies Involving BAL101533**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Date Initiated</th>
<th>Status</th>
<th>Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expansion Phase I/II oral BAL101533</td>
<td>November 2016</td>
<td>8 and 10 mg/kg cohorts complete without DLT</td>
<td>Enrollment of 20 mg/kg cohort ongoing</td>
</tr>
<tr>
<td>Phase I 48 hrs. IV BAL101533</td>
<td>August 2016</td>
<td>12 patients were administered drug, 30 and 45 mg/m² complete without DLT</td>
<td>Enrollment of 70 mg/m² is ongoing</td>
</tr>
</tbody>
</table>

*Source: Company Poster, ASCO 2017*
**Rexahn Pharmaceuticals (NYSEMKT: RNN)**

- Stable disease observed with single-agent RX-3117 in a heavily pretreated bladder cancer population.
- Part 2 has been initiated following achievement of pre-specified efficacy criteria.

**Poster:** Activity of RX-3117, an oral antimetabolite nucleoside, in subjects with metastatic bladder cancer resistant to gemcitabine: Preliminary results of a phase Ia/IIa study

Rexahn presented data from the metastatic bladder cancer portion of its open-label, single-arm, Phase Ib/IIa study using RX-3117, a cytotoxic antimetabolite that is activated by UCK2. This is a two-part study. In the first part, 10 patients with metastatic bladder cancer that are resistant to gemcitabine and 10 patients with relapsed/refractory pancreatic cancer were enrolled and received 700 mg of oral RX-3117 5 times per week on a 3 weeks on, 1 week off dosing schedule. Treatment continued for 8 cycles or until disease progression. Moving onto the second portion of the study is based on meeting prespecified criteria of 20% or more of patients in the first portion achieving PFS of at least 4 treatment cycles, or a partial/complete response in at least 10% of patients. The pancreatic cancer portion of this study advanced to the second stage of the trial back in September 2016. The presented poster for bladder cancer showed that the prespecified criteria was met with 2 patients having stable disease for 168 days, and one patient remains on treatment as of the recent data cutoff. 2 patients in the study had observed tumor shrinkage of 19% and 15%, respectively.

In the Company’s press release, Dr. Sumanta Pal, an associate professor at the City of Hope Comprehensive Cancer Center noted that prolonged stable disease is typically not seen for the enrolled patient population. Patients enrolled in this study had active progressive disease, and 70% had failed at least 3 prior lines of therapy, including 9 who failed prior gemcitabine plus cisplatin or carboplatin. Patients who are heavily pretreated typically are less responsive to subsequent therapies. Achievement of the pre-specified efficacy criteria in this patient population indicates that RX-3117 may have an anticancer effect worth exploring further. In terms of safety, treatment was overall well tolerated. The most frequent adverse events (AEs) included grade 1 diarrhea, grade 1 fatigue, grade 1 nausea, and grade 1/2 vomiting. 2 patients experienced grade 3 thrombocytopenia. Rexahn plans to enroll 10 additional patients with metastatic bladder cancer in the second part of this trial, and 2 have already been enrolled.

**Onconova Therapeutics (NasdaqGM: ONTX)**

- Bone marrow blast response correlates with an overall survival benefit in MDS patients after HMA failure treated with rigosertib.
- Phase III INSPIRE trial expected to complete enrollment with an interim analysis during the second half of 2017.

**Poster:** Relationship of bone marrow blast (BMBL) response to overall survival (OS) in a multicenter study of rigosertib (Rigo) in patients (pts) with myelodysplastic syndrome (MDS) with excess blasts progressing on or after treatment with a hypomethylating agent (HMA).

Onconova Therapeutics is primarily focused on the development of rigosertib for myelodysplastic syndromes (MDS). The drug is currently being tested in the Phase III INSPIRE trial as a treatment for patients with high-risk MDS who have failed treatment with a hypomethylating agent (HMA). The rationale for this study is based on results from the Phase III ONTIME trial, which showed in a subgroup analysis that patients under the age of 75, those who received 9 or fewer months of HMA therapy, and patients with the monosomy 7 genetic aberration had a significant difference in hazard ratios between the rigosertib plus best supportive care (BSC) and BSC arms.

Onconova reported updated data at ASCO from a single arm, open-label Phase II trial evaluating rigosertib plus best supportive care (BSC) for MDS patients who failed or relapsed after treatment with HMAs. Currently, there are no treatments approved for this patient population. 64 patients with high-risk MDS received a 72-hour continuous infusion of 1,800 mg of rigosertib/day every two weeks for 8-cycles, and every 4 weeks after. The Bone Marrow Blasts (BMBL) International Working Group (IWG) response to rigosertib was evaluated as a potential surrogate for overall survival (OS), and the best BMBL IWG response results from treatments are as follows:
- 22% (14/64) marrow complete response (mCR).
- 47% (30/64) stable disease (SD).
- 23% (15/64) progressive disease (PD).
- 8% (5/64) early death/withdrawal.

Median OS (mOS) was 7.0 month for the group as whole, and Figure 3 shows OS for the three subgroups. Landmark analysis showed that mOS in the mCR group (green) was not reached, while mOS in SD patients (blue) was 6.3 months, and 3.3 months for patients who had progressive disease (PD), in the PD (red). The results from this trial show a significant OS benefit for patients that experienced mCR (p=0.0052) compared to patients with SD or PD. Based on these results, BMBL response seems to be predictive of survival for the enrolled patient population. Onconova expects to complete enrollment in the INSPIRE study and provide an interim analysis during the second half of 2017.

![Figure 3. Overall Survival by Best Marrow Blast Response](image)

Transgene (EPA: TNG.PA)
- Preclinical data suggests further development of TG6002 in GBM.

**Abstract:** TG6002: A novel oncolytic and vectorized gene pro-drug therapy approach to treat glioblastoma.

This e-abstract was related to data with TG6002, a vaccinia virus that mainly replicates in tumor cells. TG6002 expresses FCU1, which transforms the pro-drug flucytosine (5-FC) into cytotoxic 5-fluorouracil 5-FU and 5-flur-uridilyl monophosphate (5-FUMP). The Company described the anti-tumor effects of TG6002/5-FC in U-87MG human GBM cells and in a patient derived cell line. TG6002/5-FC and TG6002 also halted cell growth to a similar degree in a xenograft glioblastoma model. In an orthotopic brain tumor model, mice survival was enhanced by intravenous TG6002 treatment, which was further augmented by oral 5-FC. Finally, TG6002 showed synergistic cytotoxic effects when combined with temozolomide in xenografted mice. As a whole, the data discussed in this abstract suggests further development of TG6002 in combination with 5-FC in GBM.

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