Turning Point Therapeutics Announces Updated Interim Clinical Data of Repotrectinib and Preclinical Data for TPX-0046, a Novel RET/SRC Inhibitor

September 3, 2019

- ***In TKI-naïve ROS1+ NSCLC Patients, Overall Response Rate by Blinded Review Improved to 91 Percent; Median Duration of Response Not Yet Mature with 20.1 months of Median Follow-Up***
- ***Improved Results in Heavily Pretreated ROS1+ NSCLC Patients, with First Confirmed Responses in Patients Treated with Two Prior TKIs***
- ***Consistent Safety Profile, with 45 Percent of ROS1+ NSCLC Patients Remaining on Treatment, including Two for More Than 24 Months***
- ***First Confirmed Response Achieved in TRK+ TKI-Naïve Patient***
- ***TPX-0046 Shows Potent Preclinical Activity in Wildtype and Mutated RET Fusions Compared to Proxy Investigational RET Inhibitors***

SAN DIEGO, Sept. 03, 2019 (GLOBE NEWSWIRE) -- Turning Point Therapeutics, Inc. (NASDAQ: TPTX), a precision oncology company developing novel drugs to address treatment resistance, today announced updated interim data from the Phase 1 portion of its ongoing Phase 1/2 TRIDENT-1 clinical study of lead drug candidate repotrectinib in patients with ROS1-positive non-small cell lung cancer (NSCLC) and TRK-positive patients with advanced solid tumors. The company also announced potent preclinical activity for its novel RET/SRC drug candidate, TPX-0046, in wild type and mutated RET fusions compared to proxy chemical compounds for investigational RET inhibitors.

“With each additional update of the ongoing Phase 1 clinical data, repotrectinib continues to encourage us with what we believe is best-in-class potential for patients with ROS1-positive advanced non-small cell lung cancer,” said Athena Countouriotis, M.D., president and chief executive officer. “The preliminary data are also encouraging in the TRK-positive population where we have treated fewer patients but today reported our first confirmed response in a TKI-naïve patient. With two ROS1-positive patients remaining on treatment for more than 2 years, we believe the results we announced today further distinguish repotrectinib, and are supportive of our ongoing, multi-cohort registrational Phase 2 TRIDENT-1 Study.

“With TPX-0046, we have demonstrated strong preclinical potency in Ba/F3 cells with the mutated KIF5B RET fusion gene and against multiple solvent front mutations that may arise from other investigational RET inhibitors and lead to treatment resistance. We believe these results position TPX-0046 for potential use in TKI-naïve patients as well as those who have developed treatment resistance with solvent front mutations. Subject to clearance of the IND, we look forward to initiating our planned clinical trial later this year.”

Repotrectinib/TRIDENT-1 Interim Update as of July 22, 2019

As of a July 22 data cut-off, the TRIDENT-1 interim update in a total of 93 patients for the overall safety analysis and 40 *ROS1+* NSCLC evaluable patients for the efficacy analysis, includes 11 patients with no prior tyrosine kinase inhibitor (TKI) treatment and 29 previously treated with at least one TKI.

Among the highlights, the company reported:

In *ROS1+* NSCLC TKI-Naïve Patients:

- One previously enrolled TKI- naïve patient responded to treatment after dose escalation to 160 mg daily, increasing the confirmed overall response rate (cORR) to 91 percent (10/11) (95% CI: 59, 100).
- Median duration of response is not yet mature in the TKI-naïve patient group with 5 of 10 (50%) responders without an event at the time of the analysis and responses ranging from 3.7+ to 23.3+ months.
- The probability of a response duration of 18 months or greater is 65 percent, estimated using the Kaplan-Meier method.
- The intracranial cORR remains 100 percent, with 3 patients in response for 14.8+, 17.6+, and 23.1 months.

In *ROS1+* NSCLC TKI-Pretreated Patients:

- Thirty-nine percent (39%) cORR across all doses (55% at the Phase 2 dose and above) in patients treated with 1 prior TKI, and 2 of the 7 responders remain in a response, both at 5.5+ months at the time of the analysis.

- Two confirmed responses among heavily pretreated patients with two prior TKIs, including one with a solvent front mutation. The cORR among 7 patients treated with 2 prior TKIs is 29 percent (95% CI: 4, 71), representing an improvement from zero responders out of 3 patients who were treated at the time of the prior data cut-off analysis.

- Among patients with known solvent front mutations, the cORR improved from the prior data cut-off to 43 percent.

In addition to the *ROS1*+ NSCLC highlights, the first confirmed response was reported in a TKI-naive *TRK*+ patient with thyroid cancer who had a duration of response of 3.8+ months at the time of the data cut-off.

The safety profile was consistent with the prior data update, with no additional dose-limiting toxicities (DLTs) or treatment-related Grade 5 events.

Preliminary Safety Analysis

A total of 93 (*ROS1+, NTRK+ and ALK+*) patients were treated with repotrectinib at dose levels from 40 mg daily (QD) to 200 mg twice daily (BID), with repotrectinib being generally well tolerated. The most frequent treatment-emergent adverse events (TEAEs) were Grade 1 or 2. The TEAEs reported in >25% of patients were dizziness (58%), dysgeusia (48%), anemia (30%), fatigue (30%), constipation (30%), dyspnea (29%), and paresthesia (29%). There were few Grade 3 treatment-related AEs (anemia (n=3); dizziness (n=3); and dyspnea, hypophosphatemia, hypoxia, lymphopenia, pleural effusion, syncope and weight increase (all n=1)), and no Grade 4 treatment-related AEs or cases of dizziness leading to treatment discontinuation.

Preliminary *ROS1*+ NSCLC Efficacy Analysis

Within the *ROS1*+ NSCLC blinded independent central review (BICR) efficacy evaluable population (n=40), the median number of prior TKI therapies was one (range 0 to 3), the majority of which were crizotinib. As of the data cut-off, 18 of 40 patients (45%) remained on treatment with two patients on repotrectinib for more than 24 months.

Efficacy results in TKI-naïve patients are summarized in the following table:

	Prior Interim Analysis by BICR March 4, 2019 Data cut-off	**Current Interim Analysis by BICR July 22, 2019 Data cut-off**
All *ROS1* NSCLC (TKI Naïve & Pretreated)	**N=33**	**N=40**
TKI Naïve	**N=11**	**N=11**
Median Follow up – (Range)	16.4 months (3.5+-19.4+)	20.1 months (5.3-24.9+)
ORR (%) (95% CI)	**9/11 (82)** (48-98)	**10/11 (91)** (59-100)
ORR at 160 mg QD or above (%)	**5/6 (83)** (5.6-17.7+)	**6/7 (86)** (3.7+-23.3+)
Median Duration of Response – Months (Range)	5 of 9 remain in cPR (10.9+ to 17.7+ months)	5 of 10 remain in cPR (3.7+ to 23.3+ months) % DOR ≥ 18 months = 65%
Intracranial ORR n (%) (95% CI)	**3/3 (100)** (29-100)	**3/3 (100)** (29-100)
Clinical Benefit Rate (%) (95% CI)**	**All remain in cPR** 11/11 (100) (72-100)	**2/3 remain in cPR** 11/11 (100) (72-100)

Efficacy results in TKI-pretreated patients are summarized in the following table:

		Prior Interim Analysis by BICR March 4, 2019 Data cut-off	**Current Interim Analysis by BICR July 22, 2019 Data cut-off**
All *ROS1* NSCLC (TKI Naïve & Pretreated)		**N=33**	**N=40**
TKI Pretreated		**N=22**	**N=29**
Median Follow up – (Range)		14.6 months (1.4-16.6+)	7.3 months (0.6-19.3+)
ORR (%) (95% CI)		**7/21 (33)** (15-57)	**9/25 (36)** (18-57)
1 or 2 prior TKIs			
	1 prior TKI	**7/18 (39)**	**7/18 (39)**
	1 prior TKI 160 mg QD or above	**6/11 (55)**	**6/11 (55)**
OR	**1 prior TKI crizotinib only 160 mg QD or above**	**4/7 (57)**	**4/7 (57)**
	2 prior TKIs	**0/3 (0)**	**2/7 (29)**
R	**3 prior TKIs**	0/1 (0)	0/4 (0)*
Duration of Response		1 prior TKI: 3 of 7 responders remain in cPR at 1.0+ to 7.6+ months	1 prior TKI: 2 of 7 responders remain in cPR (5.5+ months each) 2 prior TKIs: 2 of 2 responders remain in cPR (3.7+ months each)

G2032R Solvent Front Mutations ORR (%)	**2/5 (40)**	**3/7 (43)**
Intracranial ORR (%) **1 prior TKI**	**3/4 (75)**	**3/4 (75)**
Clinical Benefit Rate (%) **(95% CI)**** **1 or 2 prior TKIs**	15/21 (71) (48-89)	19/25 (76) (55-91)

*Includes two patients who remain in stable disease and are on treatment. This patient population is not eligible for TRIDENT-1 Phase 2 Study
**Clinical Benefit Rate: CR + PR + SD ≥ 2 Cycles

Seven patients pretreated with crizotinib had a ROS1 G2032R solvent front mutation detected at baseline by plasma cfDNA or next-generation sequencing tests. All 7 patients had tumor regressions, including 3 confirmed partial responses (cPR) in 6 patients (50%) treated at 160 mg QD or higher.

Dr. Alexander Drilon, Medical Oncologist and Research Director of the Early Drug Development Service, Memorial Sloan Kettering Cancer Center, said: “We observed consistent activity in patients with both TKI-naïve and TKI-pretreated ROS1 fusion-positive NSCLC. The drug’s tolerability profile enables long-term treatment in many patients. The data presented thus far for the TRIDENT-1 study of repotrectinib are encouraging, not only for patients with ROS1 fusion-positive cancers, but those with TRK fusion-positive cancers.”

Dr. Drilon is a principal investigator for the registrational Phase 2 portion of the TRIDENT-1 study. Repotrectinib is an investigational next-generation TKI designed to effectively target ROS1 and TRK A/B/C and systemically overcome resistant mutations that often result following treatment with other TKIs.

TPX-0046, a Novel RET/SRC Inhibitor

Preclinical studies of TPX-0046 demonstrate inhibition of wildtype and mutated RET kinases as compared to proxy chemical compounds for investigational RET inhibitors, LOXO-292 and BLU-667. In cellular assays, TPX-0046 showed comparable potency against wildtype KIF5B-RET and stronger potency against the G810R solvent front mutation.

Cell Proliferation IC_{50} (nM)

Inhibitor	Ba/F3 KIF5B-RET WT	Ba/F3 KIF5B-RET G810R (Solvent Front Mutation)	Ba/F3 KIF5B-RET V804M (Gatekeeper Mutation)
TPX-0046	0.4	16.9	533
LOXO-292	0.2	568	23.4
BLU-667	0.7	749	1.1

Data for BLU-667 and LOXO-292 based on evaluation of each corresponding proxy chemical compound purchased from commercial sources rather than from the pharmaceutical companies developing the respective kinase inhibitor.

Subject to clearance of its IND, Turning Point Therapeutics plans to initiate a clinical trial in the second half of 2019 of TPX-0046 for the treatment of advanced solid tumors harboring oncogenic RET fusions or mutations.

TPX-0046 is a multi-targeted RET and SRC kinase inhibitor with a novel three-dimensional macrocyclic structure. Activation of RET, a receptor tyrosine kinase, through gain-of-function mutations, amplifications and fusions has been found in multiple tumor types, including lung, thyroid and colon cancers. Dual inhibitor of RET and SRC represents a novel therapeutic strategy to target abnormal RET signaling in cancers. Inhibition of SRC family kinases has the potential to reduce recruitment of multiple receptor tyrosine kinases involved in bypass resistance and therefore has the potential to increase the therapeutic effect of RET inhibitors.

About Turning Point Therapeutics, Inc.
Turning Point Therapeutics is a clinical-stage precision oncology company with a pipeline of internally discovered investigational drugs designed to address key limitations of existing cancer therapies. The company’s lead program, repotrectinib, is a next-generation kinase inhibitor targeting genetic drivers of non-small cell lung cancer and advanced solid tumors. Repotrectinib, which is currently being studied in a registrational Phase 2 study, has shown antitumor activity and durable responses among kinase inhibitor treatment-naïve and pre-treated patients. Turning Point’s kinase inhibitors are designed to bind to their targets with greater precision and affinity than existing therapies, with a novel, compact structure that has demonstrated an ability to potentially overcome treatment resistance common with other kinase inhibitors. The company is driven to develop therapies that mark a turning point for patients in their cancer treatment. For more information, visit www.tptherapeutics.com.

Forward Looking Statements
Statements contained in this press release regarding matters that are not historical facts are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements include statements regarding, among other things, the efficacy, safety and therapeutic potential of repotrectinib and TPX-0046, the results, conduct and timing of Turning Point Therapeutics’ clinical trials, including the Phase 1/2 TRIDENT-1 clinical trial, plans regarding future clinical trials, and the regulatory approval path for repotrectinib. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Words such as “plans”, “will”, “believes,” “anticipates,” “expects,” “intends,” “goal,” “potential” and similar expressions are intended to identify forward-looking statements. These forward-looking statements are based upon Turning Point Therapeutics’ current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results could differ materially from those anticipated in such forward-looking statements as a result of various risks and uncertainties, which include, without limitation, risks and uncertainties associated with Turning Point Therapeutics’ business in general, and the other risks described in Turning Point Therapeutics’ filings with the SEC. All forward-looking statements contained in this press release speak only as of the date on which they were made. Turning Point Therapeutics undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

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