December 7, 2023

Zacks Small-Cap Research (NOTE)

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Allarity Therapeutics, Inc. (ALLR: NASDAQ)

ALLR: Stenoparib Clinical Update

Research Note

Early Results - Phase II Stenoparib

Allarity Therapeutics, Inc. (NASDAQ: ALLR) provided an update to investors on its Phase II study in stenoparib which is evaluating women with advanced ovarian cancer selected by the drug response predictor (DRP) diagnostic. Of 22 subjects screened, five have been enrolled and evaluated in the early read. One patient achieved a complete response and the four others experienced stable disease. Clinical benefit was observed in all subjects, with tumor shrinkage of 8% to 19% observed in the stable patients.

Exhibit I – Subject Response in Phase II Stenoparib Study[1]

Patient	Response	Tumor Shrinkage
1	Complete	100%
2	Stable Disease	19%
3	Stable Disease	11%
4	Stable Disease	8%
5	Stable Disease	8%

The study observed improved myelotoxicity for stenoparib subjects compared with other FDA approved Poly ADP-ribose polymerase inhibitors (PARPi).[2] Of the 42 evaluable women dosed stenoparib in Phase II studies, anemia (21%), neutropenia (2%) and thrombocytopenia (0%) were lower than the approved PARP inhibitor niraparib with higher observed anemia (51%), neutropenia (20%) and thrombocytopenia (52%) where n=463.

Advanced ovarian cancer patients enrolled in the study were screened using the DRP-Stenoparib CDx diagnostic. Its results rely on a transcriptomic signature consisting of 414 mRNA biomarkers that are associated with response or resistance to the drug. Each screened patient was assigned a DRP score with those over 50% selected for treatment. To date, 22 subjects were screened and 17 achieved a sufficient score to qualify for trial enrollment. Eleven women have so far been treated. Management anticipates that an interim readout, which will consist of an 8- and 16-week scan of 18 subjects, will be shared with stakeholders by March 2024.

Clinical Trial Details

The Phase II study is listed on clinicaltrials.gov under the designator NCT03878849. It is an open label, multicenter, single arm study of stenoparib (2X-121) to evaluate efficacy of the agent in 60 subjects. Oral administration of 600 mg is given daily with patients selected based on the DRP diagnostic selection criteria. The drug is given in two daily doses of 200 mg in the morning and 400 mg in the evening. All subjects enrolled had been previously treated with another PARPi and chemotherapy.

[1] Compiled from Allarity data by Zacks' analyst
[2] We note that the stenoparib population is much smaller than that of niraparib and that the measurements were made with different populations. However, the difference in prevalence between the two groups is significant enough to suggest the improved profile may continue through additional subjects in stenoparib trials.

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Stenoparib is also the subject of a 36-subject Phase I trial in combination with dovitinib. The trial (NCT05571969) dosed its first patient in March 2023 and is expected to provide a readout in 2024.

Market Dynamics

Poly ADP-ribose polymerase (PARP) inhibitors have been dominant contributors to the oncology landscape. The pharmacological class is expected to generate over $4.5 billion in sales in 2024[3] and grow in excess of 10% for the next several years. The class predominantly targets ovarian cancer but has also carved out a niche in prostate, breast and pancreatic cancers. Despite the strong showing, PARPis present several shortcomings including resistance, limited cancer focus, side effects and bioavailability. New agents that are being developed may address some of these limitations.

Exhibit II – Stenoparib PARPi Landscape[4]

Product	Owner	Stage	Response biomarker	Export Resistance (PgP mediated)	Absence of Myelotoxicity (Myelotox)	Multi-targeted (PARP/ Tankyrase)	PARP trapping	BBB penetration	Strong maintenance opportunity
Stenoparib	allarity THERAPEUTICS	Phase 2	DRP®	✓	✓	✓	✓	✓	✓
Niraparib	gsk / TESARO	Approved	Platinum response	✗	✗	✗	✓	✓	✓
Olaparib	AstraZeneca	Approved	BRCA	✗	✗	✗	✓	✗	✓
Rucaparib	pharma&	Approved	Platinum response	✗	✗	✓	✓	✗	✓
Talazoparib	Pfizer	Approved	BRCA	✓	✗	✗	✓	✗	✓
Senaparib	TopAlliance / IMPACT	Phase 3	BRCA	–	✗	✗	✓	–	✓
Veliparib	abbvie	Phase 3	BRCA	✗	✗	✗	✗	✗	✗
Pamiparib	BeiGene	Phase 2/3	BRCA	✓	✗	✗	✓	✓	✓

In response to the unmet need, there has been acquisition activity most recently by Merck KGaA (Merck Germany) that paid €160 million for ex-China rights to PARPi HRS-1167 from China's Jiangsu Hengrui Pharmaceuticals. The transaction was announced in October 2023. The primary asset acquired was the Phase I HRS-1167 which may offer improved hematologic toxicity. If the drug is successful, it may address some of the shortcomings of other PARPi including Lynparza and Zejula. Other activity in the PARPi world includes AstraZeneca launching early-stage trials for two candidates. Merck KGaA also holds an option for Nerviano Medical Sciences' NMS-293, which is also a PARPi.

There are several large pharmaceutical companies that lack a PARPi asset, including Bristol Myers Squibb, Eli Lilly, Merck (US), Gilead and others in the market tier below these mega-caps. The acquirors are seeking an asset that has overcome the shortcomings of the first generation of PARPi. Stenoparib appears to have several attractive features that may make it an attractive acquisition candidate, including improved myelotoxicity and an additional mechanism of action with tankyrase inhibition.

Stenoparib

Stenoparib is a selective inhibitor of the DNA damage repair enzymes poly-ADP-ribose polymerase (PARP) and tankyrases. PARP is a family of enzymes that are involved in multiple cellular processes including transcription, replication and DNA repair. Tankyrases also belong to the PARP family of enzymes, are implicated in cancer and involved in signaling pathways related to telomere length and vesicle trafficking among other functions. Other approved PARP inhibitors lack tankyrase inhibition, allowing stenoparib to offer a different mechanism of impeding cancer cell growth. Prior PARP inhibitor success relied on tumors that are already defective in the breast cancer (BRCA) genes. However, stenoparib activity in DRP-selected patients is not dependent on BRCA mutation status, differentiating it from the rest of the field. The synergistic inhibition of multiple DNA damage repair pathways can lead to synthetic lethality and cell death, thereby eradicating the cancer cells. Based on the research generated to date, stenoparib has demonstrated a superior therapeutic and toxicity profile and exhibits less myelotoxicity compared with other PARP inhibitors. The drug may also cross the blood brain barrier, providing additional treatment opportunities in brain metastases.

[3] Source: Evaluate Pharma Ltd., Accessed December 2023, Worldwide sales of PARPi.
[4] Allarity Corporate Presentation, December 2023.

Allarity Pipeline

Exhibit III – Allarity Pipeline[5]

		PHASE 1/1b	PHASE 2	PHASE 3	INDICATION	RIGHTS
Stenoparib	PARP & tankyrase inhibitor				2rd+ line Ovarian Cancer	Global
Stenoparib + dovitinib	PARP & tankyrase inhibitor + pan-tyrosine kinase Inhibitor				Solid Tumors	Global
Ixempra®	Microtubule inhibitor				2nd+ line Metastatic Breast Cancer	Out-licensed to Allarity in Europe (US Approved, rights held by R-Pharm U.S.)

Drug Response Predictor (DRP®) Platform

DRP is a type of precision medicine which uses genetic or molecular profiling to develop therapeutics. The approach takes into account an individual's variability in genes, environment and lifestyle, helping providers identify treatment and prevention approaches that are individually tailored.

DRP provides a systematic approach to identify patients sensitive to a particular therapy. The primary steps in the process include:

- Evaluation of an established panel of cancer cell lines that have been treated with the drug candidate:
  - The effort correlates the genetic expression profile of cell lines that are sensitive or resistant
  - The NCI-60 panel is used to identify and characterize the effectiveness of novel compounds
  - The impact of over 25,000 expressed genes is examined
- Identification of the specific mRNA & microRNA that are correlated with either response or resistance to that drug using DRP's bioinformatics algorithm
- Generation of a DRP companion diagnostic specific to the drug which identifies a subpopulation of cancer patients most likely to respond
- Validation of the DRP companion diagnostic using retrospective analysis.

In most cases, 50 to 100 biomarkers are sufficient to differentiate a tumor so that DRP can identify a drug as a matching candidate. The next step in the process is to validate the findings using retrospective data and to test the predictive capacity of the DRP. A cutoff score for patients is determined which optimizes the balance of favorable and unfavorable factors.

Summary

Allarity provided an early read on its Phase II stenoparib trial which included results for five patients. One patient achieved a complete response and all saw reductions in tumor size. These patients had failed other lines of therapy including an approved PARPi and chemotherapy. While the number of subjects is small, we expect to see an interim result in the next few months that will show whether or not the responses have persisted in a larger group.

While the small cap biotechnology space has been under pressure for some time, there are favorable signs for this group and Allarity in particular. To date, M&A activity is up 36% in terms of transactions and well over 100% in terms of dollars. Big pharma is facing revenue pressures and patent cliffs while PARPis represent a growing category. A recent PARPi transaction between Merck KGaA and Jiangsu Hengrui shows that there is interest in the class. Allarity management has indicated that they have held discussions with undisclosed pharmaceutical companies which suggests to us that a transaction could take place. A transaction could provide Allarity upfront funds and capital to advance the company's portfolio of programs. While it remains early in the Phase II stenoparib trial, the first look at data presents an encouraging outlook on future prospects.

[5] Allarity Corporate Presentation, December 2023.

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