



Arvinas Releases Interim Clinical Data Further Demonstrating the Powerful Potential of PROTAC® Protein Degraders ARV-471 and ARV-110

December 14, 2020

- ARV-471 demonstrates evidence of anti-tumor activity, and potential for best-in-class safety, and estrogen receptor (ER) degradation profile and robust efficacy signals in a heavily pretreated patient population –
- Initiation of a combination trial of ARV-471 and Ibrance® (palbociclib) expected this month; three additional trials of ARV-471 in patients with breast cancer expected to begin in 2021 –
- ARV-110 continues to demonstrate a favorable safety profile, tolerability, and anti-tumor activity in a heavily pretreated patient population as Phase 1 dose escalation continues in parallel with the ARDENT Phase 2 expansion –
- The ARDENT Phase 2 expansion trial for ARV-110 is designed to evaluate the potential for accelerated approval in a molecularly defined population and broader approval in earlier mCRPC –

NEW HAVEN, Conn., Dec. 14, 2020 (GLOBE NEWSWIRE) -- Arvinas, Inc. (Nasdaq: ARVN), a clinical-stage biopharmaceutical company creating a new class of drugs based on targeted protein degradation using its PROTAC® Discovery Engine, today announced clinical program updates for its PROTAC® protein degraders ARV-471 and ARV-110. For ARV-471, interim Phase 1 data show potential for best-in-class safety and tolerability, estrogen receptor (ER) degradation superior to that previously reported for the current standard of care agent (fulvestrant), and robust efficacy signals in heavily pretreated patients with locally advanced or metastatic ER positive / HER2 negative (ER+/HER2-) breast cancer. The efficacy signals include one Response Evaluation Criteria in Solid Tumors (RECIST) confirmed partial response (PR), two additional patients with unconfirmed PRs, and a clinical benefit rate (CBR) of 42%. For ARV-110, the ongoing dose escalation portion of the Phase 1/2 trial in men with metastatic castration-resistant prostate cancer (mCRPC) has provided additional evidence of anti-tumor activity and patient benefit, including a prostate specific antigen reduction of more than 50% (PSA50) rate of 40% in a molecularly defined patient population. Arvinas has initiated a Phase 2 dose expansion to explore a two-pronged development strategy, including the potential for accelerated approval in molecularly defined, late-line patients, and broader development in less-heavily pretreated mCRPC patients with fewer androgen receptor (AR)-independent mechanisms of tumor resistance.

Both ARV-471 and ARV-110 have been well tolerated, neither has reached a maximum tolerated dose, and the Phase 1 dose escalation trials for both programs continue. A Phase 1b combination trial of ARV-471 and Ibrance® (palbociclib) is expected to begin in December 2020, and a Phase 2 expansion cohort for ARV-471 is scheduled to begin in the first half of 2021.

"After initiating our clinical efforts just last year, we now have what we believe are clear signals of efficacy in both of our clinical-stage development programs," said John Houston, Ph.D., Chief Executive Officer at Arvinas. "The clinical benefits we've seen in both patient populations, including tumor shrinkage and low incidence of adverse effects, are compelling and reinforce our belief that our PROTAC protein degraders could dramatically change the lives of patients who have few or no therapeutic options."

"Based on data to date, we believe ARV-471 is the most promising ER-targeting therapy in the clinic, showing early signs of efficacy, a favorable tolerability profile, and better ER degradation than that previously reported for fulvestrant, the current standard of care," said Ron Peck, Ph.D., Chief Medical Officer at Arvinas. "It is exciting to see that ARV-110 continues to be active and well tolerated in what we believe is the most heavily pretreated patient population that has ever been studied with an AR-directed therapy. Our recently initiated ARDENT Phase 2 cohort expansion is specifically designed to investigate the potential of a precision medicine approach in molecularly defined, late-line patients with few available treatment options, while also fully characterizing the safety and activity of ARV-110 in earlier line patients irrespective of molecular profile, setting ARV-110 on a potential two-pronged registrational path."

ARV-471 Clinical Update

As of the data cut-off date of November 11, 2020, 21 adult patients with locally advanced or metastatic ER+/HER2- breast cancer completed at least one treatment cycle with ARV-471 (orally, once-daily) in the Phase 1 clinical trial. 100% of these patients were previously treated with a cyclin-dependent kinase (CDK) 4/6 inhibitor, 71% of patients received prior fulvestrant, and 23% of patients were pretreated with investigational selective estrogen receptor degraders (SERDs). Overall, patients had a median of five prior therapies.

In metastatic breast cancer, prior treatment with CDK4/6 inhibitors predicts high tumor ER-independence, rendering ER-targeting therapies ineffective. However, one patient in the ARV-471 trial had a confirmed PR with a 51% reduction in target lesion size as assessed by RECIST. Two additional patients had unconfirmed PRs and one additional patient demonstrated stable disease with >50% target lesion shrinkage. For evaluation of CBR, 12 patients had sufficient follow-up to be included. Five of 12 patients (42%) achieved CBR (CBR defined as PRs + complete responses + stable disease at 6 months). Three of these five patients had previously received fulvestrant, and another was treated with two investigational SERDs.

ARV-471 has been well tolerated at all dose levels, as of the data cut-off date. The most common treatment-related Grade 1-2 adverse events were nausea (24%), arthralgia (19%), fatigue (19%), and decreased appetite (14%). None of these led to discontinuation or dose reduction of ARV-471. No patients reported treatment-related Grade 3 or 4 adverse events, and no dose-limiting toxicities (DLTs) have been reported. A maximum tolerated dose (MTD) has not been reached and dose escalation continues.

The plasma exposures of ARV-471 have been dose proportional up to and including 360 mg orally once daily and have substantially exceeded Arvinas' predicted thresholds of efficacy based on preclinical studies. The estimated half-life of ARV-471 is 28 hours, supporting a once-daily schedule of administration. Analysis of five paired tumor biopsies at doses up to 120 mg provide compelling proof of mechanism for ARV-471, which has demonstrated ER degradation up to 90% (average of 62%) at those doses, while dose escalation continues.

The combined profile of ARV-471, including efficacy signals in a highly refractory population, excellent tolerability profile, and high levels of ER degradation, support a potential best-in-class ER-targeting therapy.

A Phase 2 dose expansion of ARV-471 is expected to begin in the first half of 2021. Arvinas also expects to initiate a Phase 1b cohort expansion of ARV-471 in combination with Ibrance® (palbociclib) in December 2020. This trial will evaluate the safety and tolerability of ARV-471 in combination with palbociclib and seek to identify a recommended combination dose. Arvinas expects to begin two additional studies of ARV-471 in the second half of 2021: a combination trial of ARV-471 and another targeted therapy in 2L/3L metastatic breast cancer, and a window of opportunity study in adjuvant breast cancer. The combined data from these studies will inform Arvinas' global development strategy and path forward toward the goal for ARV-471 to become the leading endocrine therapy in ER+/HER2- breast cancer.

ARV-110 Clinical Update

In the Phase 1 clinical trial in men with mCRPC, ARV-110 continues to show promising activity in a very late-line population, with PSA reductions >50% observed at doses greater than 280 mg, the last reported cohort.

In the dose escalation, ARV-110 exposures have risen dose proportionally, and at 420 mg oral daily dosing, exposures in nearly all patients have surpassed a threshold associated with tumor responses with ARV-110 in enzalutamide-resistant preclinical models of prostate cancer. Increases in exposure are associated with increased frequency of PSA reductions.

In the Phase 1 dose escalation trial, 76% of patients had been treated with prior chemotherapy, and 82% previously received both abiraterone and enzalutamide. Patients had a median of five prior lines of therapy. Multiple lines of therapy in nonmetastatic and metastatic castrate resistant prostate cancer are associated with a decreased responsiveness to AR-directed therapies and an increase in tumor heterogeneity, including in genetic mutations, which reduce the tumor's dependence on the AR signaling axis. Genetic profiling of trial patient tumors has led to significant learnings about the ARV-110 Phase 1 patient population, especially regarding genetic variability. 84% of patients in the trial have non-AR gene mutations, and as such, they would not be expected to respond. In addition, rates of specific AR mutations have been found to be higher than reported in publications that have characterized prevalence of AR mutations in men with mCRPC.

Despite the highly heterogeneous nature of the Phase 1 patient population, Arvinas has identified a molecularly defined, late-line population with a particularly strong response to ARV-110. Two of five patients (40%) with T878 or H875 mutations in AR had PSA reductions >50%, including one patient with a confirmed PR by RECIST and tumor size reduction of 80%.

In addition, two of 15 patients (13%) with wild-type AR also had PSA reductions >50%, representing activity in a broader patient population. In the full group of patients with exposures above the minimum threshold Arvinas predicted to be efficacious by preclinical studies, four of 28 (14%) had PSA reductions >50%. These PSA50 rates are higher than would be expected from approved AR-directed therapies in such late-line patients. Specifically, PSA50 response rates from standard-of-care AR-directed therapies generally decrease to 8-15% in mCRPC patients with fewer prior therapies than the patients in the ARV-110 trial.

The dual signals of ARV-110 activity in a molecularly defined population (T878/H875) and in wild-type patients supports Arvinas' two-pronged strategy for ARV-110 development and suggest a robust opportunity to address unmet need in patients with mCRPC.

A daily dose of 420 mg was selected as a Phase 2 expansion dose based on pharmacokinetics, safety profile, and the activity signals in both T878/H875 and wild-type patients. In the ARDENT Phase 2 expansion, T878/H875 patients will be enriched in a subgroup to ensure sufficient patient numbers to support the potential for accelerated approval in this population. A separate subgroup will enrich for less-pretreated patients (i.e., no prior chemotherapy and with only one previous second-generation AR-directed therapy, such as enzalutamide or abiraterone), to ensure sufficient numbers of patients whose tumors are expected to be more AR-dependent, less genetically complex, and more responsive to ARV-110.

The ARDENT Phase 2 expansion (N = ~100) began enrolling in October 2020, and Arvinas expects to provide interim data from the trial in the second half of 2021. In 2021, Arvinas also expects to begin at least one Phase 1b combination trial with a standard-of-care prostate cancer therapy and provide complete data from the Phase 1 dose escalation.

Anticipated 2020/2021 Milestones

ARV-471

- Initiation of a Phase 1b trial in combination with Ibrance® (palbociclib) (December 2020)
- Initiation of a Phase 2 dose expansion (1H21)
- Completion of the Phase 1 dose escalation (1H21)
- Safety data from the Phase 1b trial in combination with Ibrance® (palbociclib) (2H21)
- Initiation of a window of opportunity study in adjuvant breast cancer (2H21)
- Initiation of a combination trial of ARV-471 and another targeted therapy in 2L/3L metastatic breast cancer (2H21)

ARV-110

- Completion of the Phase 1 dose escalation (1H21)
- Interim data from the ARDENT Phase 2 dose expansion at 420 mg (2H21)
- Initiation of combination trial(s) with standards-of-care (2021)

Other clinical milestones

- First-in-human start for ARV-766, an AR degrader with a different profile from ARV-110 (1H21)

Arvinas Webcast Investor Meeting

Arvinas will host a conference call and webcast at 8:00 AM ET on Monday, December 14, 2020 to discuss these data. Participants are invited to listen by dialing (844) 467-7654 (domestic) or (602) 563-8497 (international) five minutes prior to the start of the call and providing the passcode 9681734. A live webcast presentation will be available [here](#) or on the Company's website at www.arvinas.com under [Events + Presentations](#). A replay of the webcast will be archived on the Arvinas website following the presentation.

About ARV-110

ARV-110 is an investigational orally bioavailable PROTAC® protein degrader designed to selectively target and degrade the androgen receptor (AR). ARV-110 is being developed as a potential treatment for men with metastatic castration-resistant prostate cancer.

ARV-110 has demonstrated activity in preclinical models of AR mutation or overexpression, both common mechanisms of resistance to currently available AR-targeted therapies.

About ARV-471

ARV-471 is an investigational orally bioavailable PROTAC® protein degrader designed to specifically target and degrade the estrogen receptor (ER) for the treatment of patients with locally advanced or metastatic ER+/HER2- breast cancer.

In preclinical studies, ARV-471 demonstrated near-complete ER degradation in tumor cells, induced robust tumor shrinkage when dosed as a single agent in multiple ER-driven xenograft models, and showed superior anti-tumor activity when compared to a standard of care agent, fulvestrant, both as a single agent and in combination with a CDK4/6 inhibitor.

About Arvinas

Arvinas is a clinical-stage biopharmaceutical company dedicated to improving the lives of patients suffering from debilitating and life-threatening diseases through the discovery, development, and commercialization of therapies that degrade disease-causing proteins. Arvinas uses its proprietary PROTAC® Discovery Engine platform to engineer proteolysis targeting chimeras, or PROTAC® targeted protein degraders, that are designed to harness the body's own natural protein disposal system to selectively and efficiently degrade and remove disease-causing proteins. In addition to its robust preclinical pipeline of PROTAC® protein degraders against validated and "undruggable" targets, the company has two clinical-stage programs: ARV-110 for the treatment of men with metastatic castrate-resistant prostate cancer; and ARV-471 for the treatment of patients with locally advanced or metastatic ER+/HER2- breast cancer. For more information, visit www.arvinas.com.

Forward-Looking Statements

This press release contains forward-looking statements that involve substantial risks and uncertainties, including statements regarding the development and regulatory status of our product candidates ARV-110, ARV-471, ARV-766, and other candidates in our pipeline, the conduct of and plans for our ongoing Phase 1/2 clinical trials for ARV-110 and ARV-471, our planned Phase 1b combination trial for ARV-471, our planned Phase 1b combination trials for ARV-110, the plans for presentation of data from our Phase 1/2 clinical trials for ARV-110 and ARV-471, the planned first-in-human start for ARV-766, and the potential advantages and therapeutic potential of our product candidates. All statements, other than statements of historical facts, contained in this press release, including statements regarding our strategy, future operations, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "might," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make as a result of various risks and uncertainties, including but not limited to: whether we will be able to successfully conduct Phase 1/2 clinical trials for ARV-110 and ARV-471 and Phase 1b combination trials for ARV-110 or ARV-471, complete our clinical trials for our other product candidates, and receive results from our clinical trials on our expected timelines, or at all, and other important factors discussed in the "Risk Factors" sections contained in our quarterly and annual reports on file with the Securities and Exchange Commission. The forward-looking statements contained in this press release reflect our current views with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this press release.

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