



ONCONOVA
THERAPEUTICS

Onconova Therapeutics' Preclinical Narazaciclib Data at SABCS Highlights Differentiated Anti-Tumor Activity v. Other CDK4/6i's

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Differentiated profile of narazaciclib supported by positive results of studies demonstrating broad multi-kinase activity, with significant anti-tumor activity and increased anti-tumor immunity, compared to approved CDK4/6 inhibitors

Data support the potential use of narazaciclib in breast and ovarian cancers

Narazaciclib progressing towards RP2D and preparation for registrational studies, with a planned update in H1 2024

NEWTOWN, Pa., Dec. 08, 2023 (GLOBE NEWSWIRE) -- [Onconova Therapeutics, Inc.](https://www.onconova.com) (NASDAQ: ONTX), ("Onconova" or "the Company"), a clinical-stage biopharmaceutical company focused on discovering and developing novel products for patients with cancer, today announced preclinical data highlighting narazaciclib's multi-kinase profile, broad anti-tumor activity and increased anti-tumor immunity, compared to palbociclib and other CDK4/6 inhibitors, in a poster presented at the San Antonio Breast Cancer Symposium (SABCS) on December 8, 2023.

"We are very pleased to share new data characterizing narazaciclib's differentiated activity, compared to palbociclib and other CDK4/6 inhibitors, especially in breast and ovarian cell lines, in a poster presentation at this year's San Antonio Breast Cancer Symposium (SABCS 2023)," said Steve Fruchtman, M.D., President and Chief Executive Officer.

Dr. Fruchtman continued, "Narazaciclib impacts a wider array of kinase targets and produced a more substantial reduction in cell viability across several large panels of breast and ovarian cell lines carrying a range of mutations, compared to palbociclib. In addition, narazaciclib treatment induced higher levels of T-cell recruiting chemokines, supporting greater anti-tumor immune activity."

"We believe that the totality of the data presented at SABCS supports narazaciclib's multi-kinase activity, its ability to target resistance pathways missed by other CDK4/6 inhibitors, and its differentiated anti-tumor and immunomodulatory activity. We hope to further demonstrate the promise of narazaciclib's differentiated profile in patients as we progress the clinical program in 2024 towards the definition of a recommended Phase 2 dose (RP2D). We are also preparing to initiate pivotal studies in the lead indication of low grade endometrioid endometrial cancer (LGEEC), and to expand into investigator-sponsored studies in breast and ovarian cancers," concluded Dr. Fruchtman.

Poster Overview

Title: Narazaciclib's differential targets and kinase inhibitory activity compared to the approved CDK4/6 inhibitors (CDK4/6is) contribute to the enhanced inhibition of tumor growth in preclinical models

Objectives: To explore the activity of narazaciclib and its metabolite, ON1232580, in comparison to the FDA-approved CDK4/6 inhibitor (CDK4/6i) palbociclib, and identify additional targets engaged by narazaciclib. Activity was measured by exposing narazaciclib and other CDK4/6 inhibitors (CDK4/6i's) to panels of resistant, mutated, or modified tumor cell lines to evaluate each agent's activity and potency to inhibit growth and reduce cell line viability.

Results:

- **Comprehensive analysis of cellular targets:** "Thermal Shift" assays affirmed that while narazaciclib and palbociclib impact a handful of similar, expected cell pathway targets, including Rb, Akt, and mTOR, narazaciclib and its main metabolite impact more kinases than palbociclib. We believe this observation could contribute to improved efficacy for narazaciclib by overcoming cancer resistance pathways not targeted by other CDK4/6i's.
- **Deeper analysis in human breast and ovarian cells/cell lines:** Using bioinformatics data from human cancer databases showed that high BUB1 kinase expression is associated with low survival in patients with breast and uterine corpus endometrial carcinomas (UCEC) and was degraded by low doses of narazaciclib. Western blot analysis of data from several breast cancer cell line panels (including those with known mutations or the overexpression of the membrane receptor, FGFR, an independent prognostic factor in some solid tumor cancers and a driver of resistance to CDK4/6 inhibitors), showed that narazaciclib and its metabolite resulted in a more substantial reduction in cell viability compared to other CDK4/6i's dosed as monotherapy or in combination with autophagy inhibitors. These data support the potential use of narazaciclib in breast cancer and UCEC, either as monotherapy or in combination with other agents.
- **Ability to induce senescence and T-cell recruiting chemokines:** Treatment with narazaciclib/metabolite produced more profound reductions in cell viability in PYMT murine breast cancer cells, compared to palbociclib and other CDK4/6i's (combined with autophagy inhibitors). In addition, narazaciclib treatment produced significantly higher increases in T-cell recruiting chemokines, including CXCL10, than palbociclib. These results suggest that narazaciclib has the differentiated

potential to promote greater levels of anti-tumor immunity, which could enhance its efficacy.

Conclusions: Expansive analysis of narazaciclib and its metabolite, compared to palbociclib and other CDK4/6i's, shows that narazaciclib has the potential to be differentiated by its:

- Multi-kinase profile, including its impact on BUB1 which is associated with poor prognosis in breast and uterine cancers;
- Potent ability to inhibit cell viability in a wide range of breast and ovarian cancer cell panels, including those with common mutations and over-expression of the FGFR, with or without autophagy inhibitors;
- Ability to produce significantly higher increases in T-cell recruiting chemokines and promote greater anti-tumor immunity.

These data support the potential use of narazaciclib in patients with breast and ovarian cancer, as well as its potential in LGEEC, based on broad, differentiated multi-kinase activity, supported by potential anti-tumor activity and anti-tumor immunity, compared to palbociclib and other CDK4/6i's. Evaluation across a range of cell lines, mutations, and prognostic factors, with or without autophagy inhibitors, underscores the strength and consistency of these data.

About Onconova Therapeutics, Inc.

Onconova Therapeutics is a clinical-stage biopharmaceutical company focused on discovering and developing novel products for patients with cancer. The Company's product candidates, narazaciclib and rigosertib, are proprietary targeted anti-cancer agents designed to disrupt specific cellular pathways that are important for cancer cell proliferation.

Narazaciclib, Onconova's novel, multi-kinase inhibitor (formerly ON 123300), is being evaluated in a Phase 1/2 combination trial with the estrogen blocker letrozole, in advanced endometrial cancer ([NCT05705505](#)). Based on preclinical and clinical studies of CDK4/6 inhibitors, Onconova believes narazaciclib has broad potential and is also evaluating opportunities for combination studies with narazaciclib and letrozole in additional indications, including breast cancer, ovarian cancer, and mantle cell lymphoma.

Rigosertib is being studied in an investigator-sponsored trial strategy to evaluate the product candidate in multiple indications, including a dose-escalation and expansion Phase 1/2a study of oral rigosertib in combination with nivolumab in patients with KRAS+ non-small cell lung cancer ([NCT04263090](#)), a Phase 2 program evaluating oral or IV rigosertib monotherapy in advanced squamous cell carcinoma complicating recessive dystrophic epidermolysis bullosa (RDEB-associated SCC) ([NCT03786237](#), [NCT04177498](#)), and a Phase 2 trial evaluating rigosertib in combination with pembrolizumab in patients with metastatic melanoma ([NCT05764395](#)).

For more information, please visit www.onconova.com.

Forward Looking Statements

Some of the statements in this release are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, Section 21E of the Securities Exchange Act of 1934, as amended, and the Private Securities Litigation Reform Act of 1995, and involve risks and uncertainties. These statements relate to Onconova's expectations regarding its clinical development and trials, its product candidates, its business and financial position. Onconova has attempted to identify forward-looking statements by terminology including "believes," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should," "preliminary," "encouraging," "approximately" or other words that convey uncertainty of future events or outcomes. Although Onconova believes that the expectations reflected in such forward-looking statements are reasonable as of the date made, expectations may prove to have been materially different from the results expressed or implied by such forward looking statements. These statements are only predictions and involve known and unknown risks, uncertainties, and other factors, including the success and timing of Onconova's clinical trials, investigator-initiated trials and regulatory agency and institutional review board approvals of protocols, Onconova's collaborations, market conditions and those discussed under the heading "Risk Factors" in Onconova's most recent Annual Report on Form 10-K and quarterly reports on Form 10-Q. Any forward-looking statements contained in this release speak only as of its date. Onconova undertakes no obligation to update any forward-looking statements contained in this release to reflect events or circumstances occurring after its date or to reflect the occurrence of unanticipated events.

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