

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): December 11, 2024

RELAY THERAPEUTICS, INC.

(Exact name of Registrant as Specified in Its Charter)

Delaware
(State or Other Jurisdiction
of Incorporation)

001-39385
(Commission File Number)

47-3923475
(IRS Employer
Identification No.)

399 Binney Street
Cambridge, Massachusetts
(Address of Principal Executive Offices)

02142
(Zip Code)

Registrant's Telephone Number, Including Area Code: (617) 370-8837

(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value \$0.001 per share	RLAY	Nasdaq Global Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Item 7.01 Regulation FD Disclosure.

On December 11, 2024, Relay Therapeutics, Inc. (the "Company") issued a press release announcing updated interim clinical data, as of a November 4, 2024 data cut-off date (the "Data Cut-off Date"), for RLY-2608, the first known allosteric, pan-mutant and isoform-selective inhibitor of phosphoinositide 3 kinase alpha ("PI3K α "), a copy of which is furnished herewith as Exhibit 99.1 to this Current Report on Form 8-K. The Company intends to host a conference call and live webcast to discuss the updated interim clinical data on December 11, 2024 at 7:00 a.m. E.T. The Company has made available a slide presentation to accompany the call, a copy of which is being furnished as Exhibit 99.2 to this Current Report on Form 8-K. The Company undertakes no obligation to update, supplement or amend the materials attached hereto as Exhibit 99.2.

The information in this Item 7.01, including Exhibit 99.1 and Exhibit 99.2 attached hereto, is intended to be furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 8.01 Other Events.

On December 11, 2024, the Company announced updated interim clinical data for RLY-2608 that were presented at the San Antonio Breast Cancer Symposium 2024.

RLY-2608 is currently being evaluated in the Company's ReDiscover Study, an ongoing first-in-human study, which was designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary antitumor activity of RLY-2608 in combination with fulvestrant, and in combination with fulvestrant and ribociclib or atimociclib.

As of the Data Cut-off Date, the RLY-2608 and fulvestrant combination arm of the study had enrolled 118 patients with PI3K α -mutated, HR+, HER2- locally advanced or metastatic breast cancer across all doses in both the dose escalation and dose expansion portions of the study, including 64 patients at the Company's recommended Phase 2 dose ("RP2D") of 600mg twice daily ("BID"). Among these 64 patients, 31 had a kinase mutation and 33 had a non-kinase mutation. Twelve patients also had a PTEN or AKT co-mutation and were therefore excluded from the efficacy analysis, consistent with the planned pivotal population.

All patients in the RLY-2608 and fulvestrant combination arm across doses had received a significant level of prior therapy in the advanced setting, including at least one prior endocrine therapy and at least one prior CDK4/6 inhibitor. Among the 64 patients who received the RP2D:

- 41% of patients (n=26) had received two or more prior lines of therapy;
- 52% of patients (n=33) had received a prior selective estrogen-receptor degrader ("SERD"), such as fulvestrant or a novel SERD;
- 25% of patients (n=16) had received chemotherapy or an ADC;
- 59% of patients (n=38) had visceral metastases; and
- 34% of patients (n=22) had a BMI of at least 30 and/or HbA1c of at least 5.7%.

Among the 52 patients in the RLY-2608 and fulvestrant combination arm who received the RP2D and did not have a PTEN or AKT co-mutation:

- The median progression free survival ("PFS") was 9.2 months for all patients and 11.4 months for second line patients;
 - o Median PFS was 11.4 months for patients with kinase mutations;
- Clinical benefit rate ("CBR") was 67% across all patients (32 of 48 CBR-evaluable patients; CBR defined as the proportion of patients with complete response, partial response or stable disease for at least 24 weeks);
- Among the 31 patients with measurable disease, 12 achieved a partial response ("PR") (39% confirmed objective response rate ("ORR"));
 - o Nearly three quarters of patients experienced tumor reductions (74%; n=23);
- Among the 15 patients with measurable disease who had a kinase mutation, two thirds achieved a PR (67% confirmed ORR; n=10); and
- Median follow-up was 9.5 months.

RLY-2608 in combination with fulvestrant was generally well tolerated in the 118 patients treated across all doses as of the Data Cut-off Date. The overall tolerability profile consisted of mostly low-grade treatment-related adverse events ("TRAEs") that were

manageable and reversible. Safety outcomes were generally as expected across dose levels based on exposure and consistent with mutant-selective PI3K α inhibition. Among the 64 patients who received the RP2D:

- The low rate of TRAE-related dose modifications allowed for 94% median dose intensity;
- Only two patients discontinued treatment due to TRAEs (Grade 1 pruritis; Grade 1 nausea, loss of appetite);
- The majority of hyperglycemia was Grade 1; only two patients (3%) experienced Grade 3 hyperglycemia; no Grade 4-5 hyperglycemia; and
- Only 31% of patients experienced a Grade 3 TRAE; no Grade 4-5 TRAEs.

The Company continues to progress two front-line triplet regimens with RLY-2608 and fulvestrant – one with the existing CDK4/6 standard-of-care, ribociclib, and one with Pfizer Inc.'s investigative selective-CDK4 inhibitor, atirmociclib. The RLY-2608, fulvestrant and ribociclib dose escalation is ongoing with biologically active doses of RLY-2608. The RLY-2608, fulvestrant and atirmociclib arm of the ReDiscover study has been initiated.

Cautionary Note Regarding Forward Looking Statements

This Current Report on Form 8-K and certain materials furnished or filed herewith contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements regarding the Company's strategy, business plans and focus; the progress and timing of the clinical development of the programs across the Company's portfolio; the expected therapeutic benefits and potential efficacy and tolerability of RLY-2608, both as a monotherapy and in combination with other agents, and its other programs, as well as the clinical data for RLY-2608; the interactions with regulatory authorities and any related approvals; the potential market opportunity for RLY-2608; the expected strategic benefits under the Company's clinical trial collaboration with Pfizer; the cash runway projection and the expectations regarding the Company's use of capital and expenses. The words "may," "might," "will," "could," "would," "should," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" and similar words or expressions, or the negative thereof, are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, risks associated with: the impact of global economic uncertainty, geopolitical instability and conflicts, or public health epidemics or outbreaks of an infectious disease on countries or regions in which the Company has operations or does business, as well as on the timing and anticipated results of its clinical trials, strategy, future operations and profitability; the delay or pause of any current or planned clinical trials or the development of the Company's drug candidates; the risk that the preliminary or interim results of its preclinical or clinical trials may not be predictive of future or final results in connection with future clinical trials of its product candidates and that interim and early clinical data may change as more patient data become available and are subject to audit and verification procedures; the Company's ability to successfully demonstrate the safety and efficacy of its drug candidates; the timing and outcome of its planned interactions with regulatory authorities; and obtaining, maintaining and protecting its intellectual property. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the Company's most recent Annual Report on Form 10-K and Quarterly Report on Form 10-Q, as well as any subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent the Company's views only as of today and should not be relied upon as representing its views as of any subsequent date. The Company explicitly disclaims any obligation to update any forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

Item 9.01 Financial Statements and Exhibits.

99.1	Press release issued by Relay Therapeutics, Inc. on December 11, 2024, furnished herewith.
99.2	Corporate presentation, dated December 11, 2024, furnished herewith.
104	Cover Page interactive Data File (embedded within Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

RELAY THERAPEUTICS, INC.

Date: December 11, 2024

By: /s/ Brian Adams
Brian Adams
Chief Legal Officer



Relay Therapeutics Announces Updated Interim Data for RLY-2608 + Fulvestrant Demonstrating Continued Maturation of Clinically Meaningful Progression Free Survival

New interim data show 11.4-month median PFS in 2L patients with PI3K α -mutated, HR+/HER2- metastatic breast cancer at RP2D

39% confirmed ORR across all patients & 67% in patients with kinase mutations at RP2D

Data support planned initiation of 2L pivotal study in 2025

Next-generation triplet combination with atirmociclib (CDK4-selective) initiated & ribociclib triplet combination ongoing

Relay Therapeutics to host a conference call today, December 11, at 7am ET (6am CT)

San Antonio, Tex. – December 11, 2024 – Relay Therapeutics, Inc. (Nasdaq: RLAY), a clinical-stage precision medicine company transforming the drug discovery process by combining leading-edge computational and experimental technologies, today announced updated interim clinical data for RLY-2608, the first known investigational allosteric, pan-mutant and isoform-selective inhibitor of PI3K α . The updated data show a median progression free survival (PFS) of 11.4 months in second line (2L) patients with PI3K α -mutated, HR+, HER2- locally advanced or metastatic breast cancer who received RLY-2608 600mg twice daily (BID) + fulvestrant. These data are being presented today at the San Antonio Breast Cancer Symposium (SABCS) 2024.

“These updated data help build on previously reported results that show a level of benefit that had not previously been seen with non-selective PI3K α inhibitors,” said Don Bergstrom, M.D., Ph.D., President of R&D at Relay Therapeutics. “We are particularly encouraged to see even greater benefit observed in the patients in which we are working to start a pivotal study next year; in these 2L patients, RLY-2608 + fulvestrant demonstrated a median progression free survival that is more than twice that of the existing standards-of-care.”

ReDiscover – RLY-2608 First-in-Human Study

RLY-2608 is currently being evaluated in ReDiscover, an ongoing first-in-human study, which was designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary antitumor activity of RLY-2608 in combination with fulvestrant, and in combination with fulvestrant and ribociclib or atirmociclib (Pfizer’s selective CDK4 inhibitor).

The RLY-2608 + fulvestrant arm of the study, as of the November 4, 2024 interim data cut-off for this arm, had enrolled 118 patients with PI3K α -mutated, HR+, HER2- locally advanced or metastatic breast cancer across all doses in both the dose escalation and dose expansion portions of the study, including

64 patients at the company's recommended Phase 2 dose (RP2D) of 600mg BID. Among these 64 patients, 31 had a kinase mutation and 33 had a non-kinase mutation. Twelve patients also had a PTEN or AKT co-mutation and were therefore excluded from the efficacy analysis, consistent with the planned pivotal population.

The RLY-2608 + ribociclib + fulvestrant arm of the study continues to enroll patients with PI3K α -mutated, HR+, HER2- locally advanced or metastatic breast cancer in dose escalation. The RLY-2608 + atimociclib + fulvestrant arm of the study has recently been initiated.

Patients were Heavily Pre-Treated

All RLY-2608 + fulvestrant patients across doses had received a significant level of prior therapy in the advanced setting, including at least one prior endocrine therapy and at least one prior CDK4/6 inhibitor. Among the 64 patients who received the RP2D:

- 41% of patients (n=26) had received two or more prior lines of therapy
- 52% of patients (n=33) had received a prior selective estrogen-receptor degrader (SERD), such as fulvestrant or a novel SERD
- 25% of patients (n=16) had received chemotherapy or an ADC
- 59% of patients (n=38) had visceral metastases
- 34% of patients (n=22) had a BMI of at least 30 and/or HbA1c of at least 5.7%

Promising Efficacy Data in Proposed Pivotal Population

Among the 52 RLY-2608 + fulvestrant patients who received the RP2D and did not have a PTEN or AKT co-mutation:

- The median PFS was 9.2 months for all patients and 11.4 months for 2L patients
 - Median PFS was 11.4 months for patients with kinase mutations
- Clinical benefit rate (CBR) was 67% across all patients (32 of 48 CBR-evaluable patients; CBR defined as the proportion of patients with complete response, partial response or stable disease for at least 24 weeks)
- Among the 31 patients with measurable disease, 12 achieved a partial response (PR) (39% confirmed objective response rate, ORR)
 - Nearly three quarters of patients experienced tumor reductions (74%; n=23)
- Among the 15 patients with measurable disease who had a kinase mutation, two thirds achieved a PR (67% confirmed ORR; n=10)
- Median follow-up was 9.5 months

Maintained Meaningfully Differentiated Tolerability Profile

RLY-2608 + fulvestrant was generally well tolerated in the 118 patients treated across all doses as of the data cut-off date. The overall tolerability profile consisted of mostly low-grade treatment-related adverse events (TRAEs) that were manageable and reversible. Safety outcomes were generally as expected across dose levels based on exposure and consistent with mutant-selective PI3K α inhibition. Among the 64 patients who received the RP2D:

- The low rate of TRAE-related dose modifications allowed for 94% median dose intensity
- Only two patients discontinued treatment due to TRAEs (Grade 1 pruritis; Grade 1 nausea, loss of appetite)
- The majority of hyperglycemia was Grade 1; only two patients (3%) experienced Grade 3 hyperglycemia; no Grade 4-5 hyperglycemia
- Only 31% of patients experienced a Grade 3 TRAE; no Grade 4-5 TRAEs

Continued Progression of Front-Line Breast Cancer Regimens

Two front-line triplet regimens are being progressed – one with the existing CDK4/6 standard-of-care ribociclib and one with Pfizer’s investigative selective-CDK4 inhibitor atirmociclib. RLY-2608 + ribociclib + fulvestrant dose escalation is ongoing with biologically active doses of RLY-2608. The RLY-2608 + atirmociclib + fulvestrant arm of the ReDiscover study has been initiated.

Anticipated RLY-2608 Next Steps

- Breast Cancer:
 - Initiate 2L pivotal study of RLY-2608 + fulvestrant in 2025
 - Disclose complete Phase 1/2 data in 2025
- Vascular Malformations:
 - Initiate vascular malformations study in the first quarter of 2025

Cash balance will be operationalized to preserve ability to complete 2L pivotal study

As of the end of the third quarter of 2024, cash, cash equivalents and investments were approximately \$840 million.

Conference Call Information

Relay Therapeutics will host a conference call and live webcast today, December 11, 2024, at 7:00 a.m. ET (6:00 a.m. CT). Registration and dial-in for the conference call may be accessed through Relay Therapeutics’ website under Events in the News & Events section through the following link: <https://ir.relaytx.com/news-events/events-presentations>. An archived replay of the webcast will be available following the event.

The data presentation from the San Antonio Breast Cancer Symposium is also available on the Relay Therapeutics website in the “Publications/Presentations” section through the following link: <https://relaytx.com/pipeline/>.

About RLY-2608

RLY-2608 is the lead program in Relay Therapeutics' efforts to discover and develop mutant selective inhibitors of PI3K α , the most frequently mutated kinase in all cancers, with oncogenic mutations detected in about 14% of patients with solid tumors. RLY-2608 has the potential, if approved, to address more than 300,000 patients per year in the United States, one of the largest patient populations for a precision oncology medicine.

Traditionally, the development of PI3K α inhibitors has focused on the active, or orthosteric, site. The therapeutic index of orthosteric inhibitors is limited by the lack of clinically meaningful selectivity for mutant versus wild-type (WT) PI3K α and off-isoform activity. Toxicity related to inhibition of WT PI3K α and other PI3K isoforms results in sub-optimal inhibition of mutant PI3K α with reductions in dose intensity and frequent discontinuation. The Dynamo[®] platform enabled the discovery of RLY-2608, the first known allosteric, pan-mutant, and isoform-selective PI3K α inhibitor, designed to overcome these limitations. Relay Therapeutics solved the full-length cryo-EM structure of PI3K α , performed computational long time-scale molecular dynamic simulations to elucidate conformational differences between WT and mutant PI3K α , and leveraged these insights to support the design of RLY-2608. RLY-2608 is currently being evaluated in a first-in-human study designed to treat patients with advanced solid tumors with a PIK3CA (PI3K α) mutation. For more information on RLY-2608, please visit [here](#).

About Relay Therapeutics

Relay Therapeutics is a clinical-stage precision medicine company transforming the drug discovery process by combining leading-edge computational and experimental technologies with the goal of bringing life-changing therapies to patients. As the first of a new breed of biotech created at the intersection of complementary techniques and technologies, Relay Therapeutics aims to push the boundaries of what's possible in drug discovery. Its Dynamo[®] platform integrates an array of leading-edge computational and experimental approaches designed to drug protein targets that have previously been intractable or inadequately addressed. Relay Therapeutics' initial focus is on enhancing small molecule therapeutic discovery in targeted oncology and genetic disease indications. For more information, please visit www.relaytx.com or follow us on Twitter.

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cash runway projection and the expectations regarding Relay Therapeutics' use of capital and expenses. The words "may," "might," "will," "could," "would," "should," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" and similar words or expressions, or the negative thereof, are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, risks associated with: the impact of global economic uncertainty, geopolitical instability and conflicts, or public health epidemics or outbreaks of an infectious disease on countries or regions in which Relay Therapeutics has operations or does business, as well as on the timing and anticipated results of its clinical trials, strategy, future operations and profitability; the delay or pause of any current or planned clinical trials or the development of Relay Therapeutics' drug candidates; the risk that the preliminary or interim results of its preclinical or clinical trials may not be predictive of future or final results in connection with future clinical trials of its product candidates and that interim and early clinical data may change as more patient data become available and are subject to audit and verification procedures; Relay Therapeutics' ability to successfully demonstrate the safety and efficacy of its drug candidates; the timing and outcome of its planned interactions with regulatory authorities; and obtaining, maintaining and protecting its intellectual property. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in Relay Therapeutics' most recent Annual Report on Form 10-K and Quarterly Report on Form 10-Q, as well as any subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Relay Therapeutics' views only as of today and should not be relied upon as representing its views as of any subsequent date. Relay Therapeutics explicitly disclaims any obligation to update any forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

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RELAY[®]
THERAPEUTICS

2024 SABCS – RLY-2608 Data Update
December 2024

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements regarding Relay Therapeutics' strategy, business plans and focus; the progress and timing of the clinical development of the programs across Relay Therapeutics' portfolio; the expected therapeutic benefits and potential efficacy and tolerability of RLY-2608, both as a monotherapy and in combination with other agents, and its other programs, including lirafugratinib as well as the clinical data for RLY-2608; the interactions with and approval of regulatory authorities and any related approvals; the potential market opportunity for RLY-2608; and the expected strategic benefits under Relay Therapeutics' clinical trial collaboration with Pfizer; the cash runway projection and the expectations regarding Relay Therapeutics' use of capital and expenses. The words "may," "might," "will," "could," "would," "should," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" and similar words or expressions, or the negative thereof, are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Any forward-looking statements in this presentation are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, risks associated with: the impact of global economic uncertainty, geopolitical instability and conflicts, or public health epidemics or outbreaks of an infectious disease on countries or regions in which we have operations or do business, as well as on the timing and anticipated results of our clinical trials, strategy, future operations and profitability; the delay or pause of any current or planned clinical trials or the development of our drug candidates; the risk that the preliminary or interim results of our preclinical or clinical trials may not be predictive of future or final results in connection with future clinical trials of our product candidates and that interim and early clinical data may change as more patient data become available and are subject to audit and verification procedures; our ability to successfully demonstrate the safety and efficacy of our drug candidates; the timing and outcome of our planned interactions with regulatory authorities; and obtaining, maintaining and protecting our intellectual property. These and other risks, uncertainties and important factors are described in the section entitled "Risk Factors" in our most recent Annual Report on Form 10-K and Quarterly Report on Form 10-Q, as well as any subsequent filings with the Securities and Exchange Commission. Any forward-looking statements represent our views only as of the date of this presentation and we undertake no obligation to update or revise any forward-looking statements, whether as a result of new information, the occurrence of certain events or otherwise. 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. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party studies, publications, surveys and other data to be reliable as of the date of this presentation, we have not independently verified, and make no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent source has evaluated the reasonableness or accuracy of our internal estimates or research and no reliance should be made on any information or statements made in this presentation relating to or based on such internal estimates and research.

This presentation contains trademarks, trade names and service marks of other companies, which are the property of their respective owners

1

ReDiscover Trial Update – RLY-2608 + Fulvestrant Doublet Data

- Dr. Sammons – overview of evolving treatment landscape
- Data summary

2

RLY-2608 – Other Updates

3

Next steps

RLY-2608 data presented at 2024 San Antonio Breast Cancer Symposium

PI3K α mutations represent a large commercial opportunity

Breast Cancer

~140k pts
(prevalence¹)

Vascular Malformations

~170k pts
(prevalence²)

Non-Breast Cancer Solid Tumors

~90k pts
(incidence³)

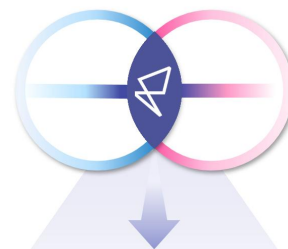
Non-selective PI3K α targeting has significant limitations

— Challenging Tolerability

— Limited Efficacy

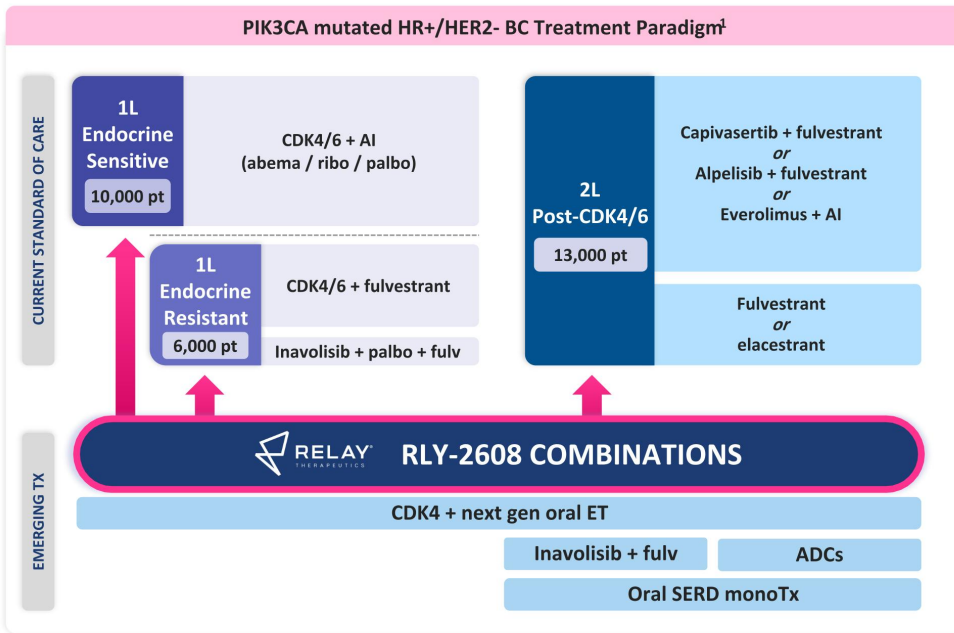
— Limited Combinability

Relay Tx's Dynamo[®] Platform created mutant selective molecule



RLY-2608

1. Prevalent US patient population with a PIK3CA mutation in each line of therapy, excluding PTEN co-mutations (Global Data HR+/HER2- Breast Cancer Global Forecast, November 2023; 3rd party source for alteration rate); 2. Prevalent US patient population of vascular malformation patients with a PIK3CA mutation (multiple sources); 3. Incident US patient population solid tumors annually with a PIK3CA mutation, excluding PTEN and KRAS co-mutations (SEER; 3rd party source for alteration rate, May 2024)



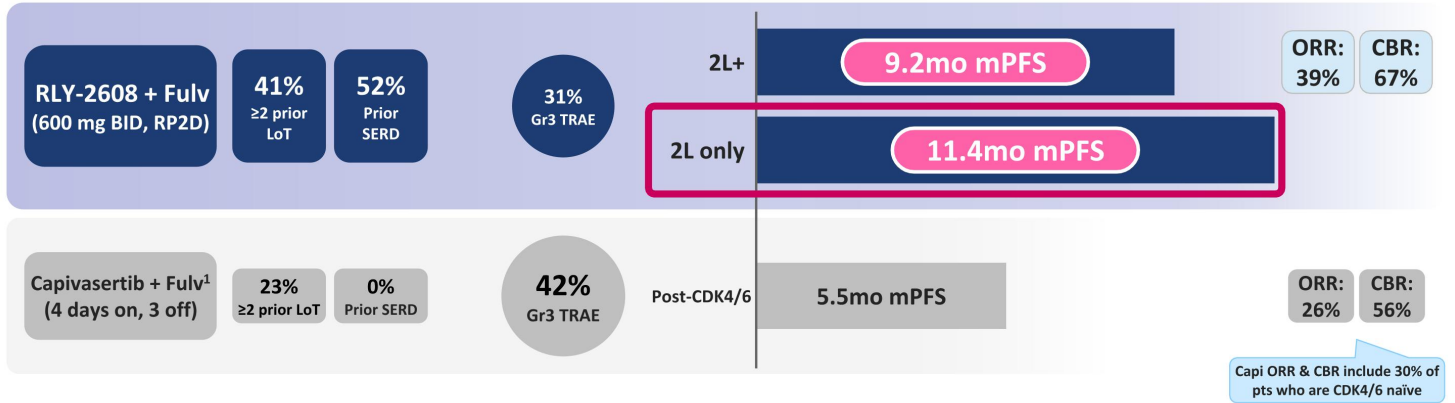
\$6B+
 Current PI3K α Pathway
 Total Addressable Market²
*(Metastatic HR+/HER2-
 Breast Cancer)*

1. Prevalent US patient population with a PIK3CA mutation in each line of therapy, excluding PTEN co-mutations (Global Data HR+/HER2- Breast Cancer Global Forecast, November 2023; 3rd party source for alteration rate); 2. Relay Tx PIK3CA internal market forecast (patient-based – US, EU5, Japan). Forecast includes estimates for genetic testing, class share, market access, compliance, duration of therapy and assumes current PIK3CA therapy net price (primary sources: SEER; GloboCan; Global Data; Evaluate Pharma; DRG Market Forecast; PIK3CAI PIs)
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More Heavily
Pre-Treated Pt

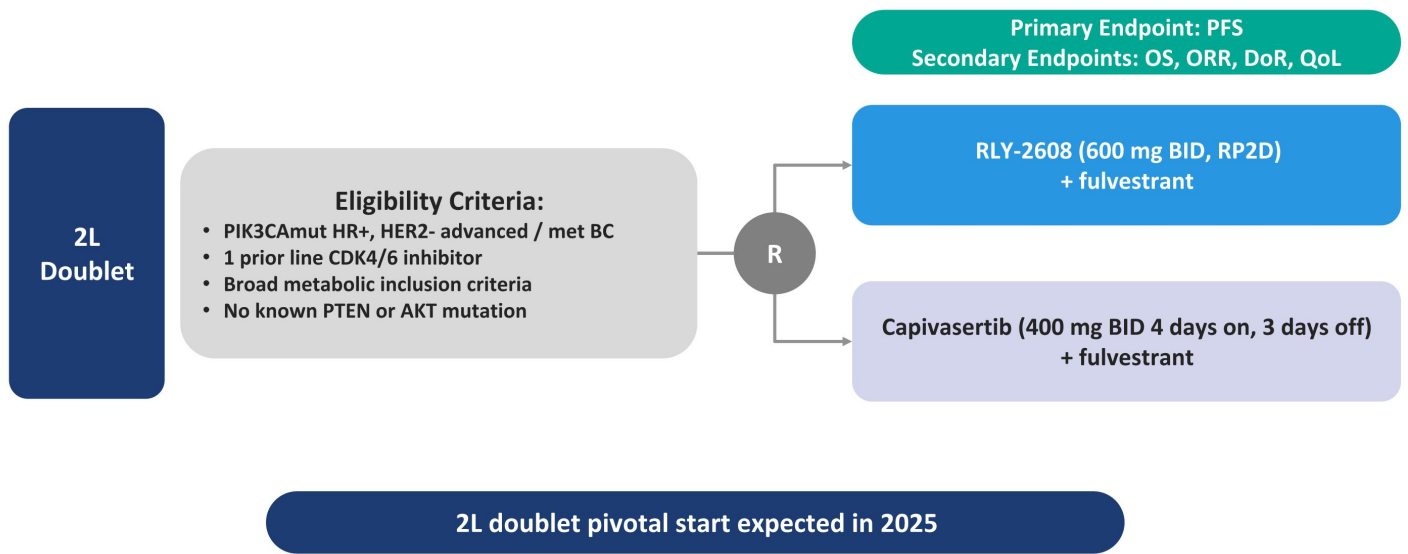
Favorable
Tolerability

Favorable Efficacy
*PIK3CA*mut, HR+/HER2- Advanced / Metastatic Breast Cancer (post CDK4/6)

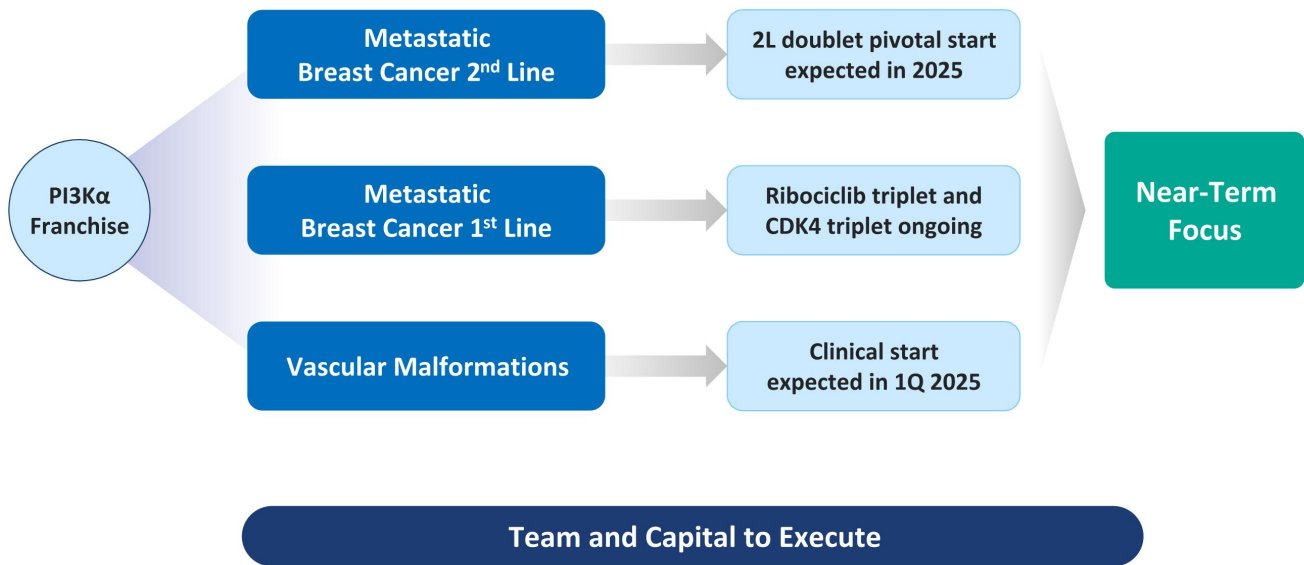


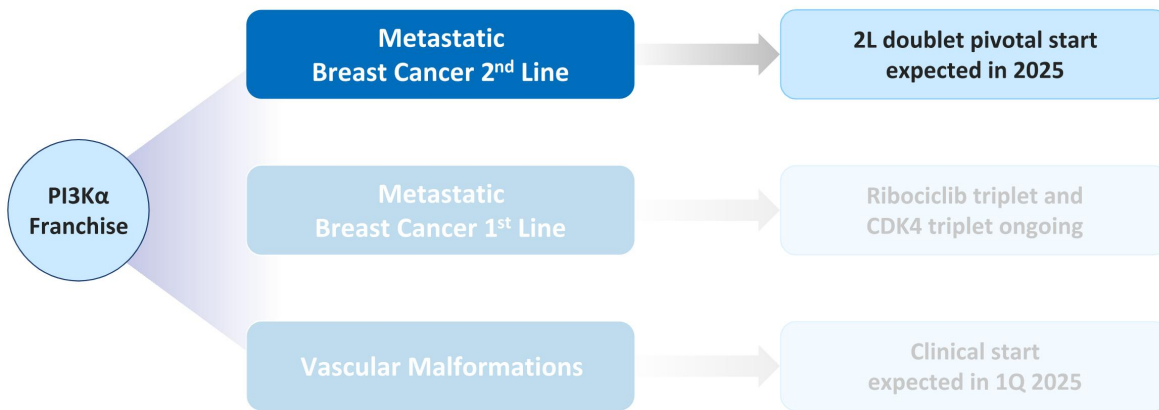
Interim RLY-2608 safety and efficacy data supportive of pivotal trial in 2L Breast Cancer against capivasertib

1. CAPitello-291: Turner N Engl J Med 2023; 388:2058-2070; 2. In CAPitello-291, CBR and ORR not reported for CDK4/6-experienced patient population; ORR = objective response rate, mPFS = median progression free survival, LoT = line of therapy (metastatic setting), SoC = Standard of Care, TRAE = treatment related adverse effects, RP2D = recommended Phase 2 dose, CBR = clinical benefit rate, SERD = selective estrogen receptor degrader; Note: data shown are not from head-to-head studies, and no head-to-head studies have been conducted. ReDiscover preliminary data as of 11/04/2024 6

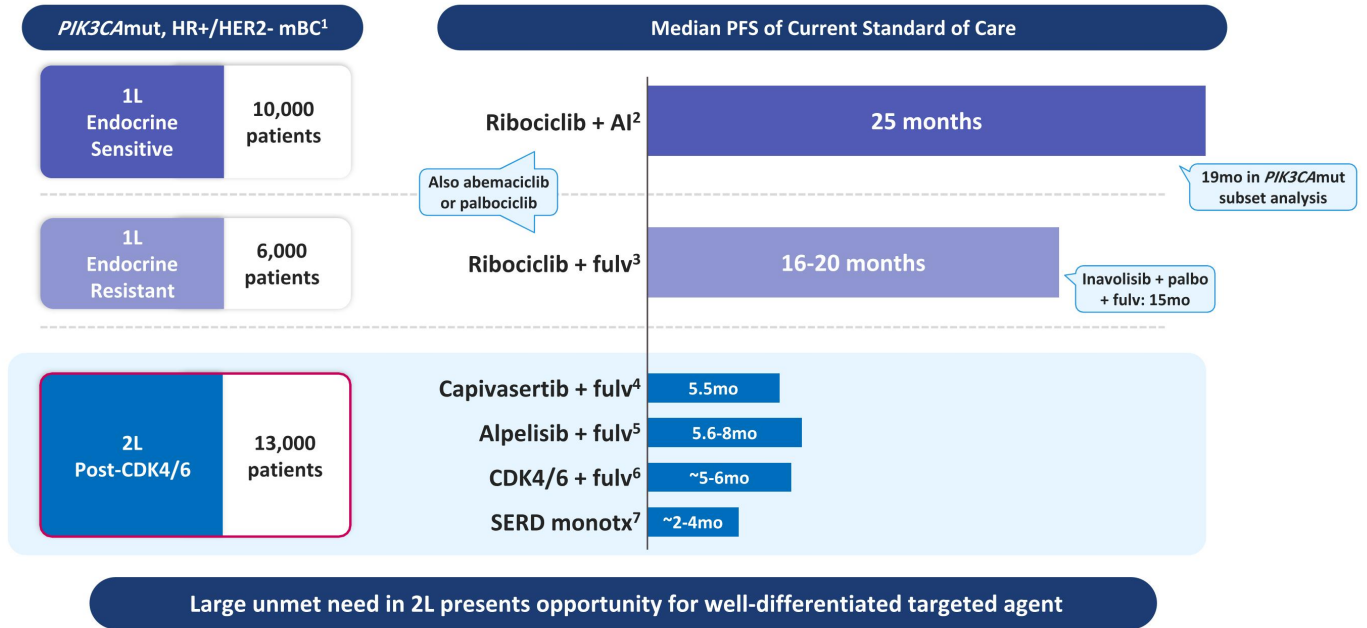


*Subject to discussions with regulators; eligibility criteria, endpoints, RP2D, and other aspects of trial design have not yet been finalized; OS = overall survival, DoR = duration of response, QoL = quality of life, met BC = metastatic Breast Cancer; 2L = 2nd line
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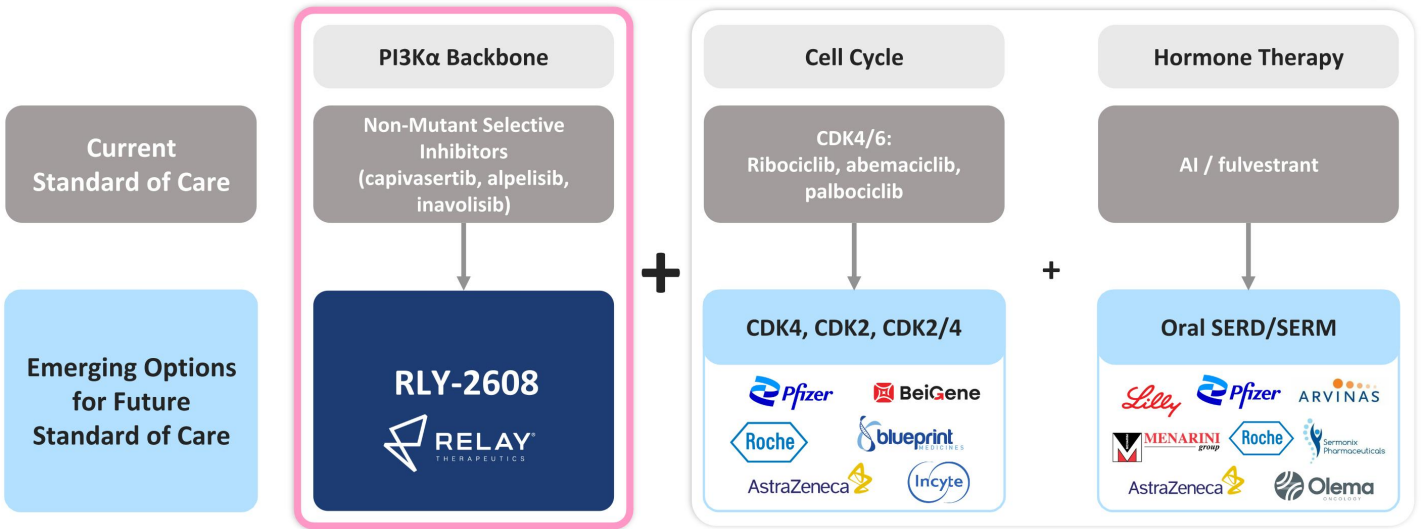


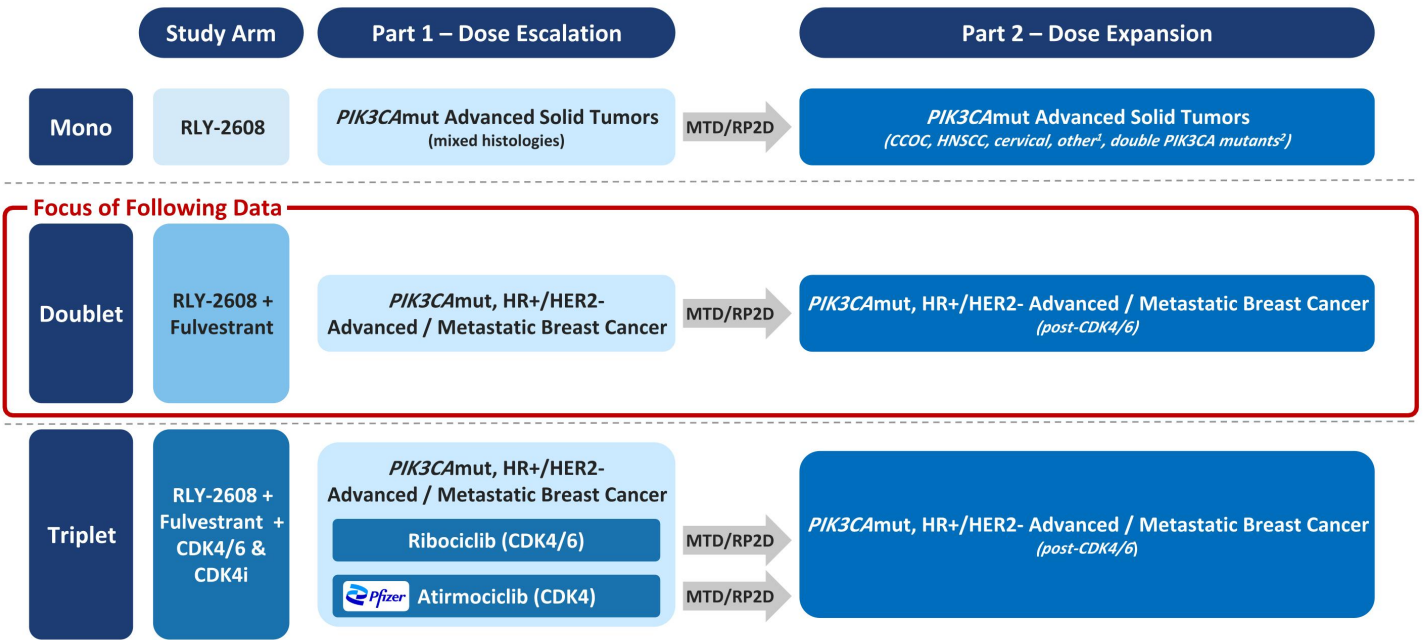
Team and Capital to Execute



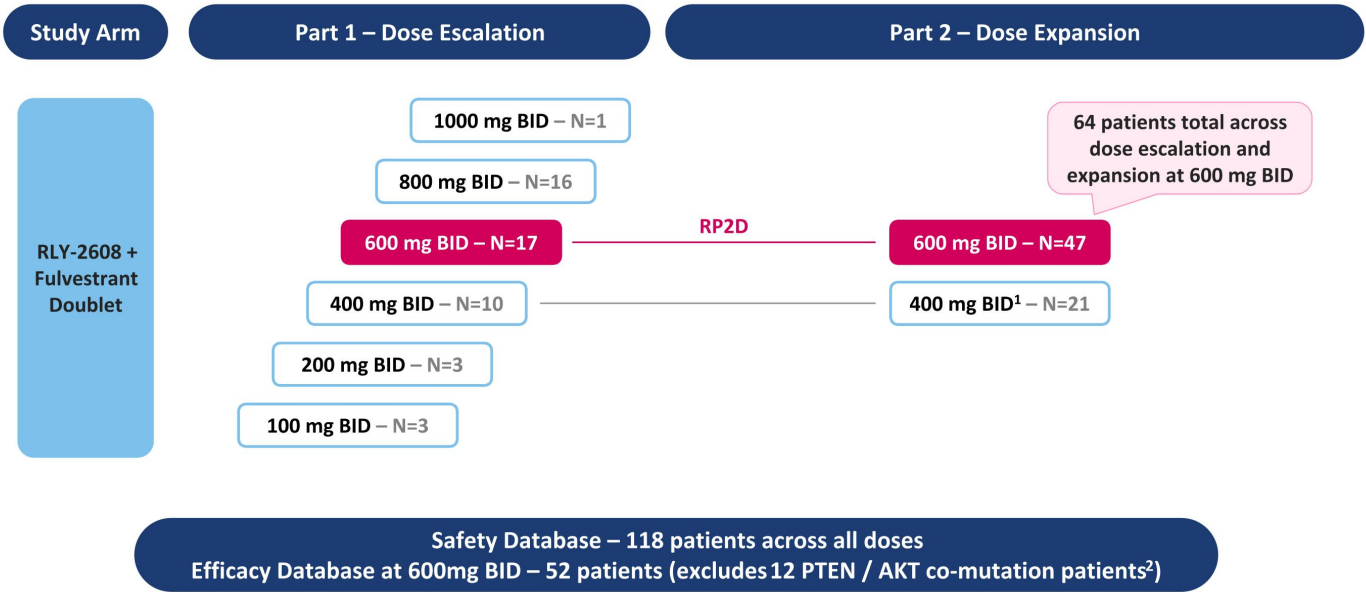
Notes: 1. Prevalent US patient population with a PIK3CA mutation in each line of therapy, excluding PTEN co-mutations (Global Data HR+/HER2- Breast Cancer Global Forecast, November 2023; 3rd party source for alteration rate); 2. All-comers and PIK3CAmut sub-group, MONALEESA-2; 3. All-comers and PIK3CAmut sub-group, MONALEESA-3; 4. Turner N Engl J Med 2023; 388:2058-2070 (n=355); 5. Rugo 2021 Lancet Oncol 22:489, SABCS 2021 #P1-18-03; 6. MAINTAIN: Kalinsky 2023 J Clin Oncol 41:4004, postMONARCH; Kalinsky 2024 ASCO; 7. Elacestrant Prescribing Information
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*PIK3CA*mut HR+/HER2- Breast Cancer Treatment Paradigm





1. Excludes *PIK3CA*mut clear cell OvCA, HNSCC, Cervical cancer, and colorectal patients; 2. Double mutation defined as one major *PIK3CA* mutation (E542X, E545X, H1047X) + ≥1 additional *PIK3CA* mutation per local assessment; CCOC = clear cell ovarian cancer
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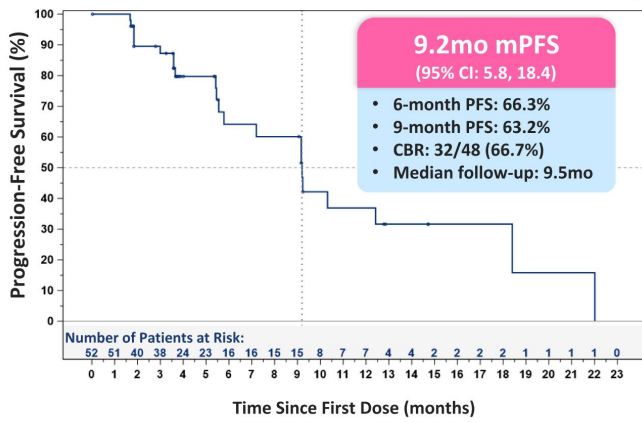
1. 400mg cohort is not yet mature for efficacy analysis. Full Phase I results, including 400mg cohort, will be disclosed at a later date; 2. As defined by central ctDNA
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	RLY-2608 + Fulvestrant	
	All Patients (N=118)	600 mg BID (RP2D, N=64)
Age, Median (Range), Years	59.0 (34, 85)	59.0 (34, 80)
ECOG, 0 / 1, n (%)	69 (58.5) / 49 (41.5)	38 (59.4) / 26 (40.6)
Local PIK3CA Baseline Results		
Kinase Mutation, n (%)	57 (48.3)	31 (48.4)
Non-Kinase Mutations, n (%)	61 (51.7)	33 (51.6)
BMI ≥30 or HbA1c ≥5.7%, n (%)	44 (37.3)	22 (34.4)
Measurable Disease, n (%)	83 (70.3)	42 (65.6)
Patients with Visceral Metastases, n (%) ¹	75 (63.6)	38 (59.4)
Prior Lines of Therapy in Advanced Setting		
1, n (%)	62 (52.5)	38 (59.4)
2+, n (%)	56 (47.5)	26 (40.6)
Prior Therapies in Advanced Setting		
CDK4/6, n (%) ²	118 (100.0)	64 (100.0)
Fulvestrant or Novel SERD, n (%)	66 (55.9)	33 (51.6)
Chemo / ADC, n (%)	30 (25.4)	16 (25.0)
ESR1 Mutation (Central Read) ³ , n (%)	40 (35.4)	18 (28.6)

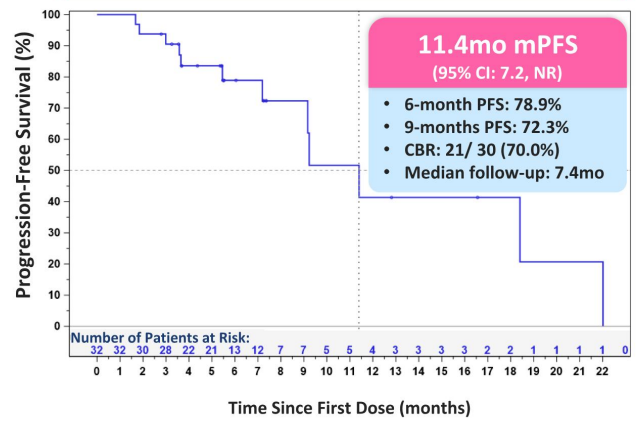
1. Visceral metastatic sites include brain, lung, liver, pleural, peritoneal involvement; 2. Three patients received prior CDK4/6 in the adjuvant setting which is allowed per protocol; 3. Percentage was based on pts with evaluable ctDNA data at baseline; ECOG = Eastern Cooperative Oncology Group performance status

RLY-2608 600 mg BID (RP2D) + Fulvestrant
 Excluding PTEN / AKT Co-Mutations

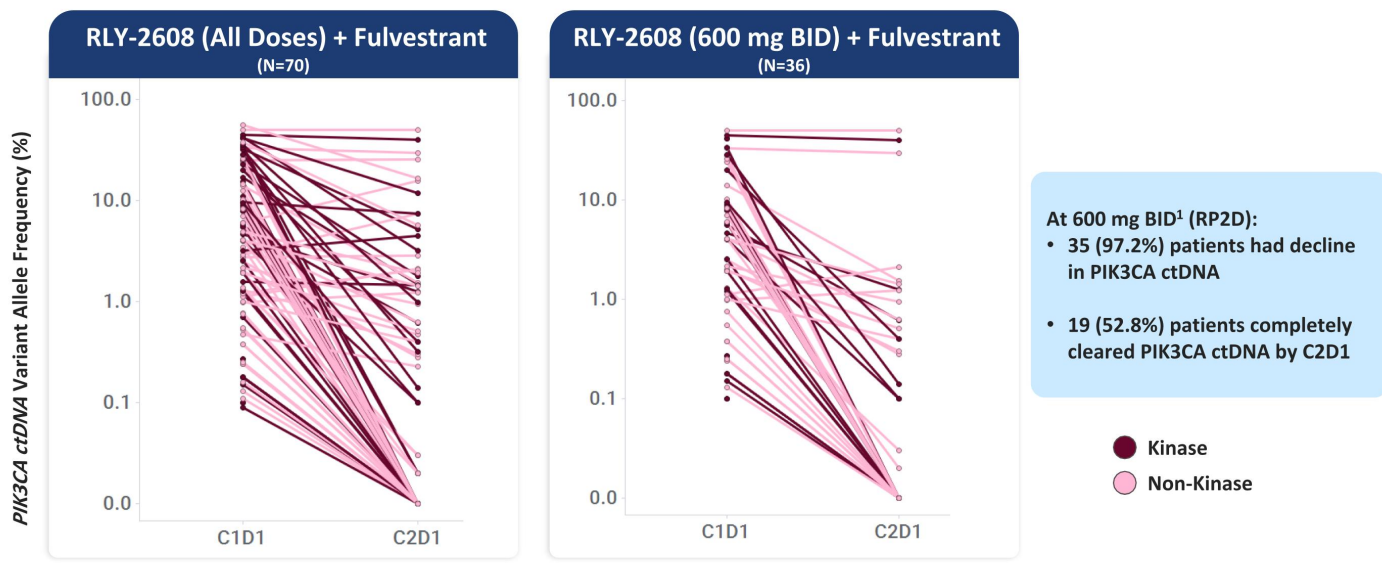
All Patients (N=52)



2L Patients (N=32)

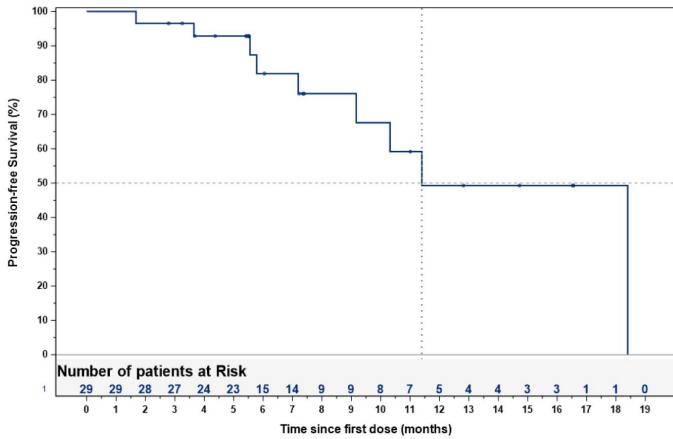


Note: Follow-up estimated based on reversed KM. PFS estimates based on KM methods.
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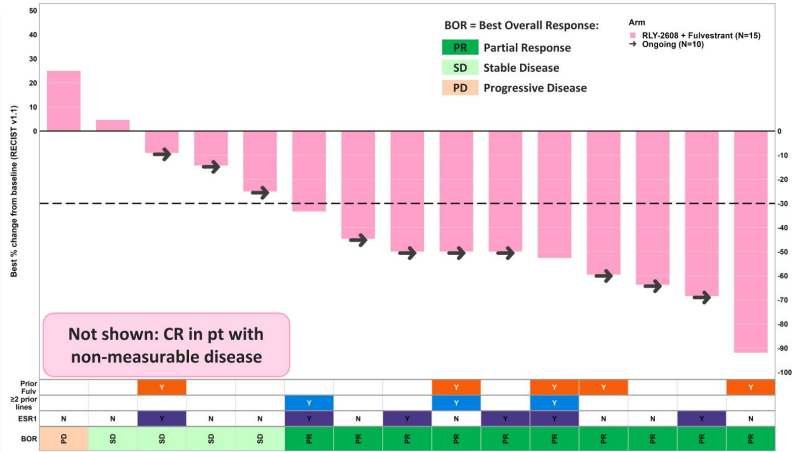
1. N=36 patients without PTEN/AKT co-alterations who have detectable PIK3CA at baseline and a paired C1D1-C2D1 ctDNA result are presented
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RLY-2608 600 mg BID (RP2D) + Fulvestrant
Excluding PTEN / AKT co-mutations (N=29)



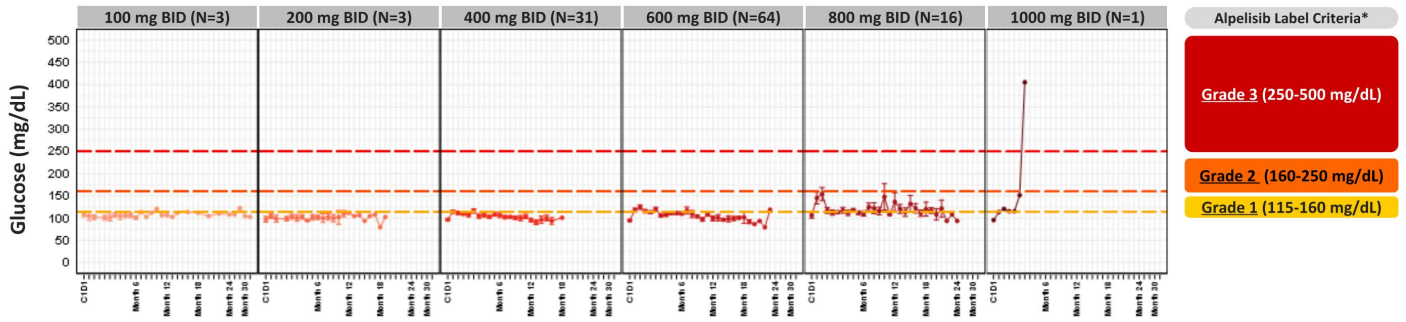
11.4 mo mPFS
(95% CI: 9.2, NR)

RLY-2608 600 mg BID (RP2D) + Fulvestrant
Excluding PTEN / AKT – Measurable Disease (N=15)



66.7% ORR
(10/15 pt, 95% CI: 38.4%, 88.2%)

RLY-2608 + Fulvestrant



Note: *Based on CTCAE version 4 criteria
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		All Patients (N=118)		600mg BID (RP2D, N=64)	
		All Gr	Gr3	All Gr	Gr3
Any TRAE		92.4%	25.4%	93.8%	31.3%
TRAEs ≥15% of 600 mg BID	Hyperglycemia¹	42.4%	2.5%	46.9%	3.1%
	Nausea	41.5%	0.8%	50.0%	1.6%
	Fatigue¹	40.7%	8.5%	35.9%	9.4%
	Creatinine Increased	34.7%	0.8%	34.4%	1.6%
	Diarrhea	30.5%	1.7%	35.9%	3.1%
	Decreased Appetite	16.9%	0%	20.3%	0%
	Headache	15.3%	0.8%	20.3%	0%
	Hypokalaemia¹	15.3%	1.7%	17.2%	1.6%
	Vomiting	12.7%	0%	15.6%	0%
Other select TRAEs	Rash¹	11.9%	0.8%	10.9%	1.6%
	Stomatitis	3.4%	0.8%	4.7%	0%

27% Gr1 hyperglycemia (no intervention required)

No Gr4-5 TRAEs

¹: Hyperglycemia includes the MedDRA v26.0 Preferred Terms (PT): Hyperglycemia, Blood Glucose Increased, Glucose Tolerance Impaired; Fatigue includes the PTs: Fatigue, Asthenia; Hypokalemia includes the PTs: Hypokalemia and blood potassium decreased; Rash includes the PTs: Rash, Rash Macular, Rash Maculo-Papular

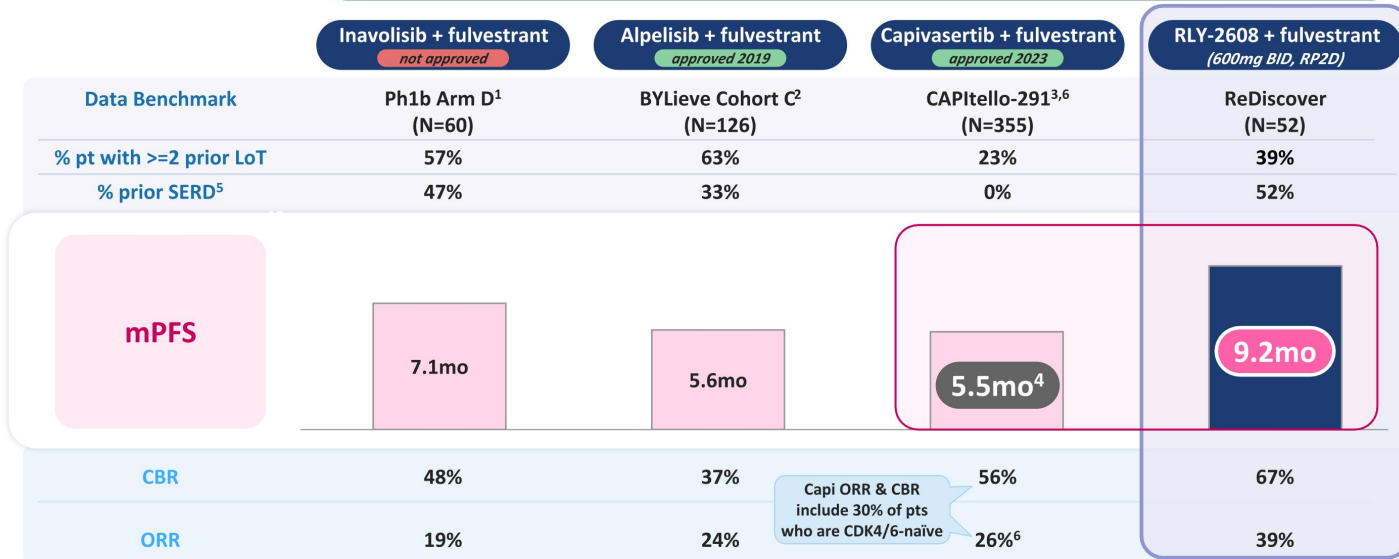
		All Patients (N=118)	600mg BID (RP2D, N=64)
Dose Intensity	Relative Dose Intensity (%), Median	97%	94%
Dose Modifications Due to TRAE	Dose Reduction, n (%)	38 (32.2)	25 (39.1)
	Dose Interruption, n (%)	56 (47.5)	33 (51.6)
	Dose Discontinuation, n (%)	7 (5.9)	2 (3.1)
TRAEs Leading to Dose Reduction	Fatigue ¹	12 (10.2)	6 (9.4)
	Blood Creatinine Increased	8 (6.8)	3 (4.7)
	Diarrhea	6 (5.1)	3 (4.7)

Grade 1 pruritis; Grade 1 nausea and loss of appetite

Maintained 94% dose intensity with very low TRAE discontinuations at 600mg BID

Note: 1. Fatigue includes the PTs: Fatigue and Asthenia; TRAEs leading to Dose Reduction in more than 2 patients within 600 mg BID are presented.
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Doublet Combination Regimens

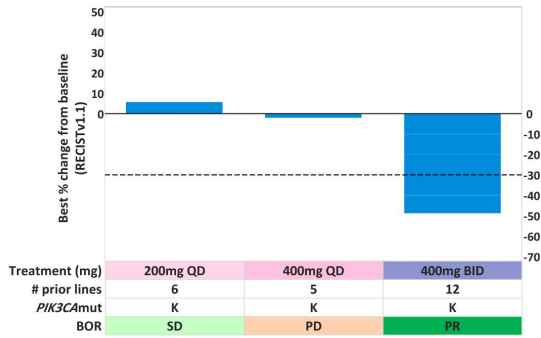


1. SABCS 2021 #P5-17-05 (n=60); 2. SABCS 2021 #PD-13-05; 3. Turner N Engl J Med 2023; 388:2058-2070 (n=355); 4. 5.5mo mPFS reported in CDK4/6-experienced patient sub-population of CAPitello-291; 5. Prior SERD includes fulvestrant and next-generation SERDs; 6. FDA Prescribing Information.
 Note: These data are derived from different clinical trials at different points in time, with differences in molecule composition, trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.
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RLY-2608 Active as Monotherapy

Relay Tx Focus on Significant Commercial Opportunities

All HR+/HER2- Breast Cancer Patients Across All Doses (N=3)*



**ORR: 1/3
(33%)**

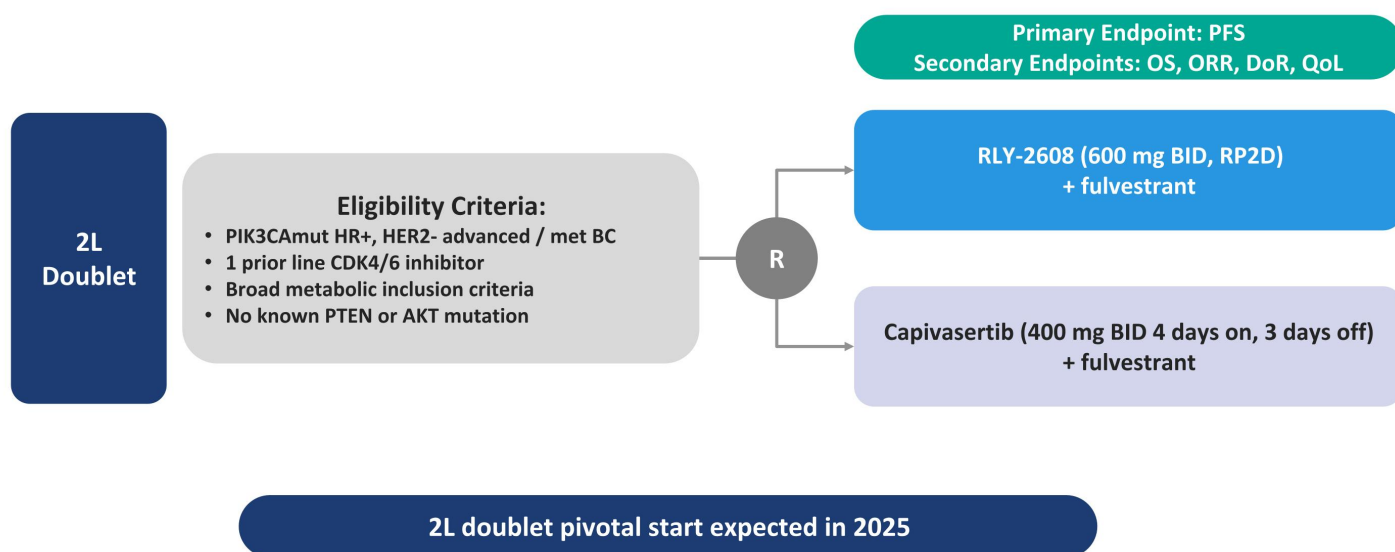
**DCR: 2/3
(67%)**

No endometrial patients dosed*

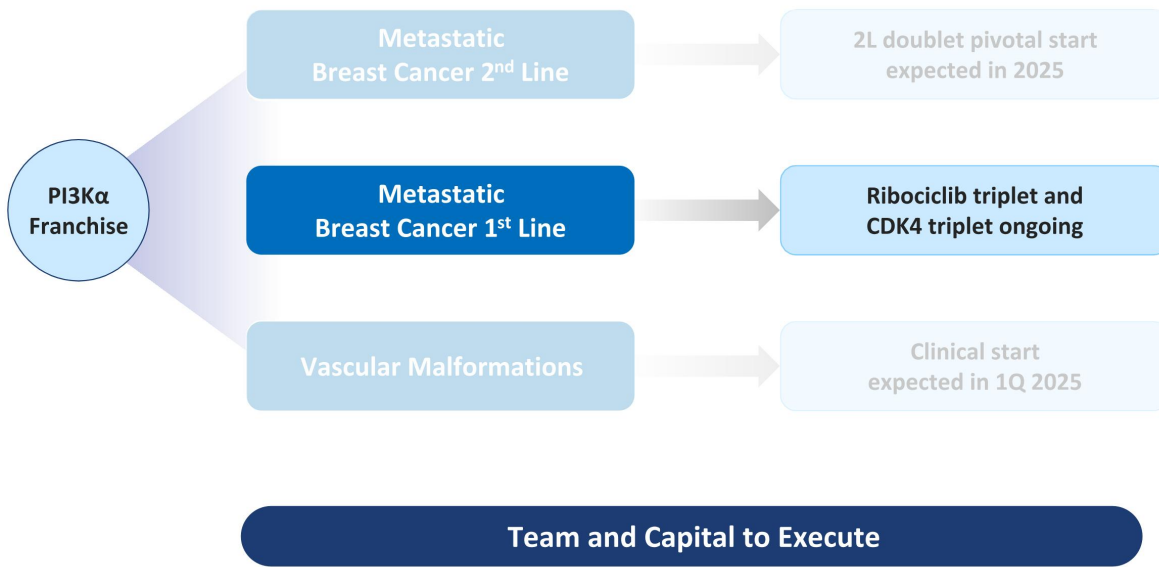
2L Breast Cancer	13,000 pt
1L Breast Cancer	Endocrine Sensitive 10,000 pt
	Endocrine Resistant 6,000 pt
Vascular Malformations	170,000 pt

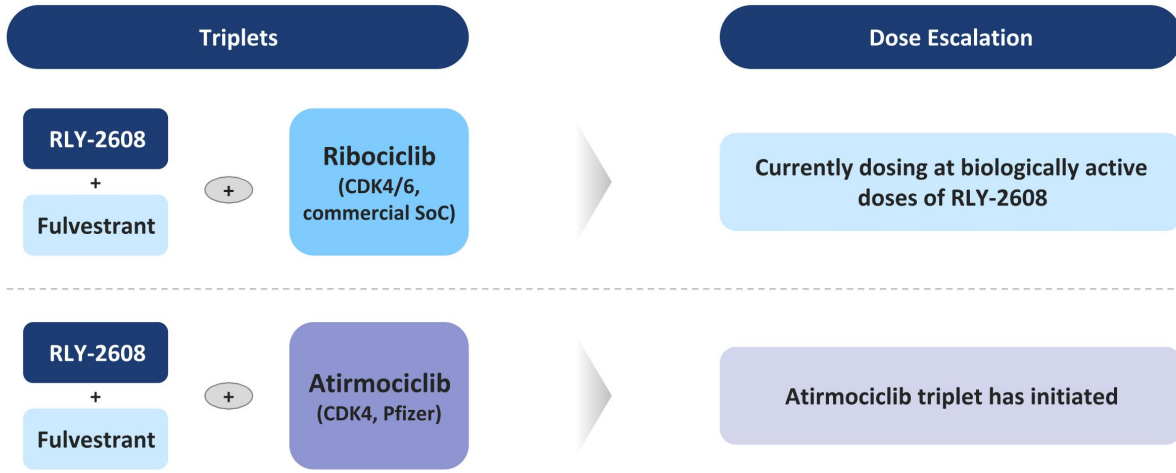
BC combinations & VMs are near-term development focus; other solid tumor development currently deprioritized

* Within efficacy evaluable population, which excludes PTEN co-mutated patients
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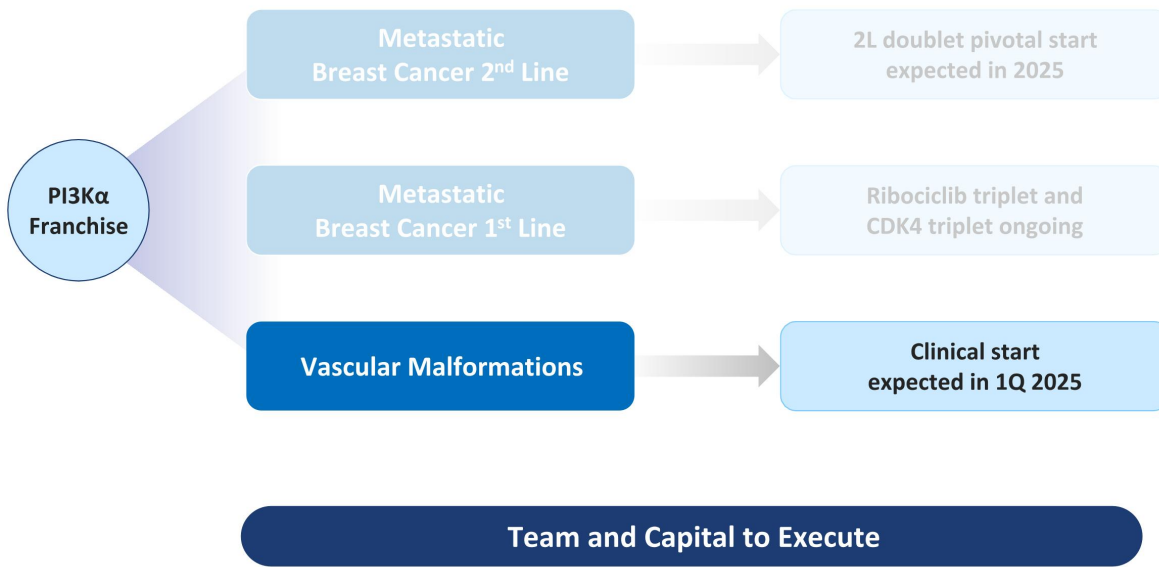


*Subject to discussions with regulators; eligibility criteria, endpoints, RP2D, and other aspects of trial design have not yet been finalized; OS = overall survival, DoR = duration of response, QoL = quality of life, met BC = metastatic Breast Cancer; 2L = 2nd line
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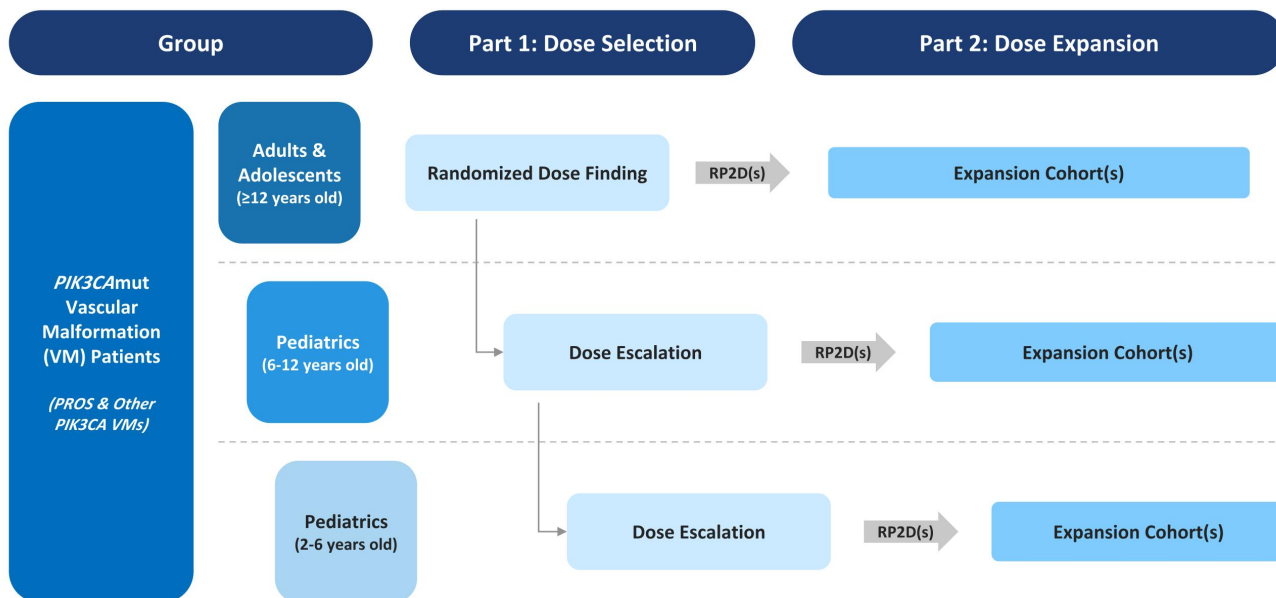


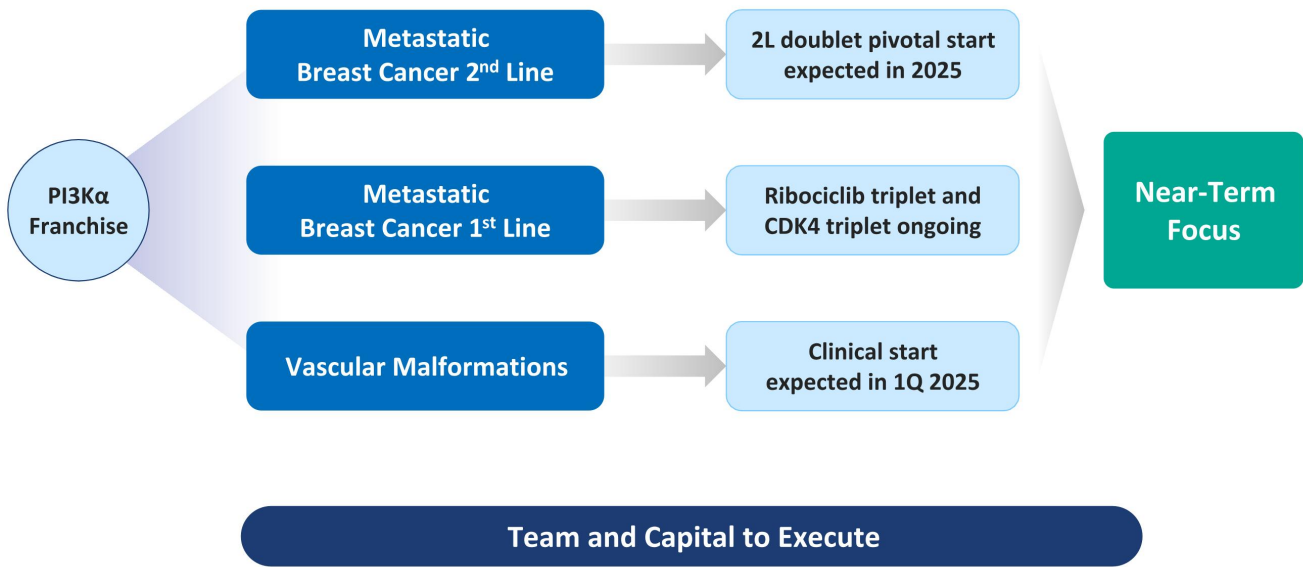
Phase 1 Aim for Triplets: Demonstrate safety, tolerability and preliminary efficacy with both current generation CDK4/6 and next-gen CDK4 to enable pivotal development potential in both



Vascular Malformation Types					
	PIK3CA-Related Overgrowth Spectrum (PROS)	Lymphatic Malformation (LM)	Venous Malformation (VM)	Cerebral Cavernous Malformation (CCM)	
US Patients	~5-15k	~80k	~100k	~120k	Total US pt across types >300k pt ~170k pt PIK3CAmut
% PIK3CAmut	100% ~5-15k pt	80% ~65k pt	~20-25% ~20-25k pt	40-55% ~50-65k pt	
Approved Therapies	Vioice® (alpelisib)	No approved systemic therapy			

Sources: ISSVA classification, NORD, Mayo Clinic, Novartis, Penington et al 2023, Gallagher et al 2022, Luks et al 2015, Limaye et al 2015, Peyre et al 2021, Hong et al 2021. Photo sources: Venot et al. Nature 2018, Wenger et al Genet Med 2022, Limaye et al Nature Genetics 2008, Mayo Clinic © 2024 Relay Therapeutics





Doublet Combination Regimens

Inavolisib + fulvestrant
not approved

Alpelisib + fulvestrant
approved 2019

Capivasertib + fulvestrant
approved 2023

RLY-2608 + fulvestrant
(600mg BID, RP2D)

Data Benchmark

Ph1b Arm D¹
(n=60)

BYLieve²
(n=127)

FDA Label³
(n=355)

ReDiscover
(n=64)

All Grade 3+ TRAEs



33%



62%



42%⁴



31%

Grade 3+
Hyperglycemia



22%



29%



2%



3%

Dose Discontinuation
due TRAEs

0%



18%



10%



3%

Discontinuous dosing:
4 days on, 3 days off

34% of pt BMI \geq 30
and/or HbA1c \geq 5.7%

1. SABCS 2021 #P5-17-05; 2. Rugo 2021 Lancet Oncol 22:489; 3. FDA Prescribing Information; 4. CAPitello-291: Turner N Engl J Med 2023; 388:2058-2070.

Note: These data are derived from different clinical trials at different points in time, with differences in molecule composition, trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted. ReDiscover preliminary data as of 11/04/2024 31

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Data Benchmark

Ph1b Arm D¹
(n=60)

BYLieve²
(n=127)

FDA Label³
(n=355)

ReDiscover
(n=64)

HbA1c Enrollment Criteria

<7%

≤6.4%

<8%⁴

<7%

34% of pt
BMI ≥30
and/or
HbA1c ≥5.7%

Gr1-2 Gr3+

Hyperglycemia

40% 22% 62%

30% 29% 59%

17% 2% 19%

27% 17% 3% 47%

Diarrhea

42%

54% 6% 60%

65% 12% 77%

33% 3% 36%

Rash⁵

12%

19% 10% 29%

41% 15% 56%

2% 11%

Stomatitis

25%

28% 3% 31%

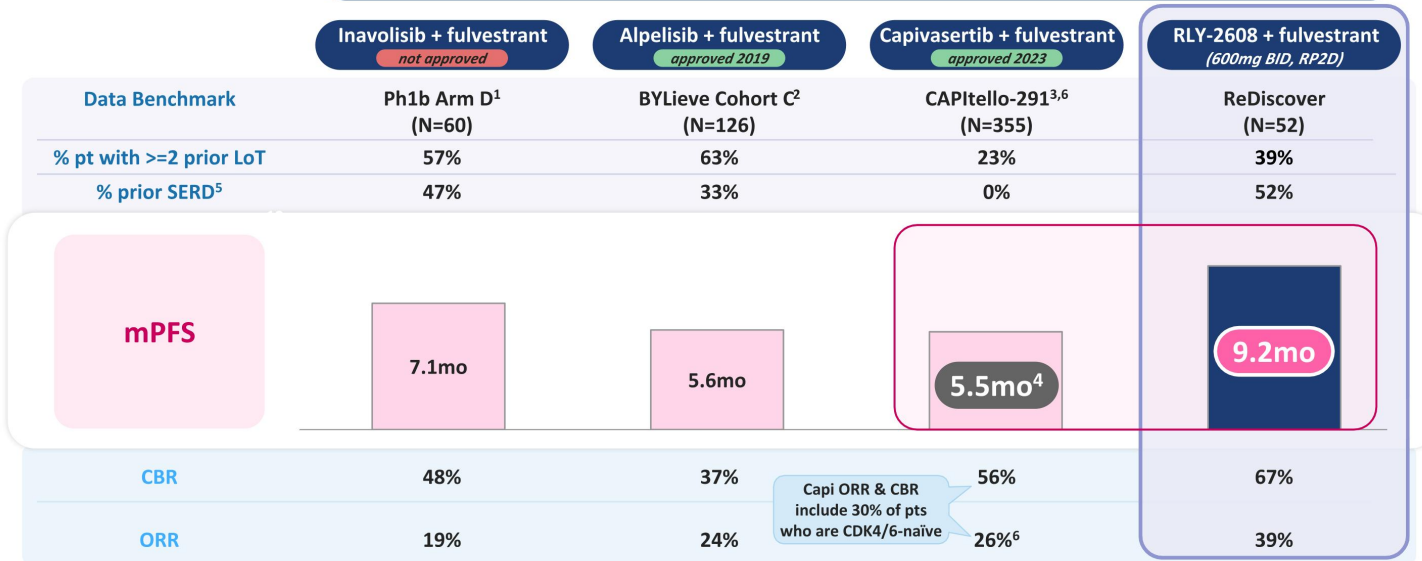
23% 2% 25%

9%

5%

1. SABCS 2021 #P5-17-05; 2. Rugo 2021 Lancet Oncol 22:489; 3. FDA Prescribing Information; 4. per CAPitello-291 enrollment criteria; 5. Rash for capivasertib references Cutaneous Adverse Reactions grouped term includes a number of preferred terms listed in FDA Prescribing Information.
Note: These data are derived from different clinical trials at different points in time, with differences in molecule composition, trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.

Doublet Combination Regimens



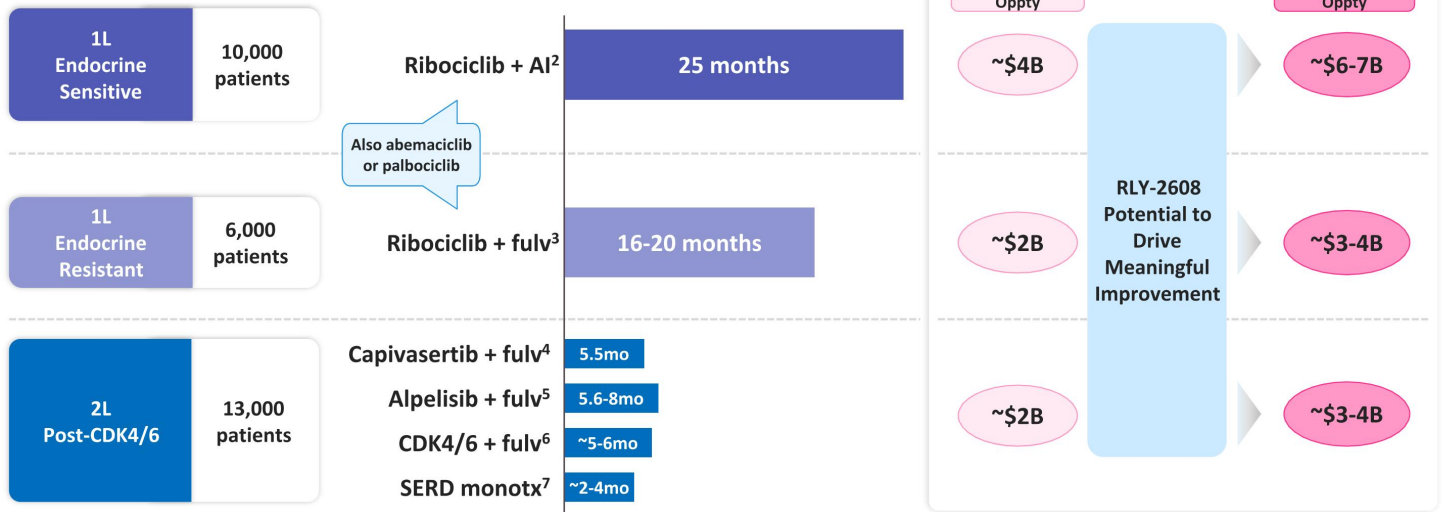
1. SABCS 2021 #P5-17-05 (n=60); 2. SABCS 2021 #PD-13-05; 3. Turner N Engl J Med 2023; 388:2058-2070 (n=355); 4. 5.5mo mPFS reported in CDK4/6-experienced patient sub-population of CAPitello-291; 5. Prior SERD includes fulvestrant and next-generation SERDs; 6. FDA Prescribing Information.
 Note: These data are derived from different clinical trials at different points in time, with differences in molecule composition, trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.
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Large Unmet Need in Metastatic Breast Cancer

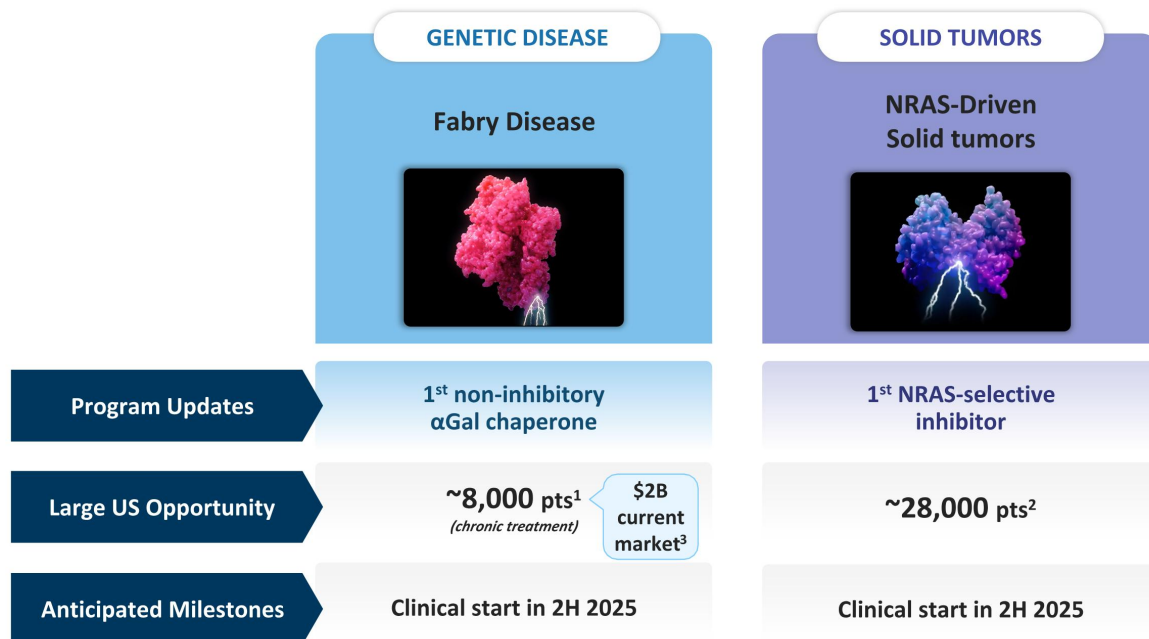
PIK3CAmut, HR+/HER2- mBC¹

Median PFS of Current Standard of Care

Potential Market Opportunity⁸



Notes: 1. Prevalent US patient population with a PIK3CA mutation in each line of therapy, excluding PTEN co-mutations (Global Data HR+/HER2- Breast Cancer Global Forecast, November 2023; 3rd party source for alteration rate); 2. All-comers and PIK3CAmut sub-group, MONALEESA-2; 3. All-comers and PIK3CAmut sub-group, MONALEESA-3; 4. Turner N Engl J Med 2023; 388:2058-2070 (n=355); 5. Rugo 2021 Lancet Oncol 22:489, SABCS 2021 #P1-18-03; 6. MAINTAIN: Kalinsky 2023 J Clin Oncol 41:4004, postMONARCH; Kalinsky 2024 ASCO; 7. Elacestrant Prescribing Information; 8. Informed by qualitative and quantitative primary market research performed in Q2 2024



1. Prevalence of Fabry patients, 2025 (National Fabry Disease Foundation, Nov 2024); 2. Newly diagnosed (incident) solid tumors with an NRAS mutation, excluding melanoma stages 0-II (SEER, 3rd party source for alteration rate, Jan 2024); 3. Fabry disease forecasted 2024 market size per EvaluatePharma, includes Galafold® and ERTs (May 2024)
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	Target	Program	Preclinical	Early Clinical	Late Clinical	
BREAST CANCER	PI3K α	Endocrine Tx (ET) doublet				
		RLY-2608 (PI3K α^{PAN})	Ribociclib + ET triplet			
			CDK4i + ET triplet			
		<i>Other Novel Combinations</i>				
	CDK2	RLY-2139				
ER α	RLY-1013 (Degradar)					
GENETIC DISEASE	Fabry Disease	α Gal Chaperone				
	Vascular Malformations	RLY-2608 (PI3K α^{PAN})				
		Other PI3K α^{PAN}				
SOLID TUMORS	NRAS	NRAS-selective Inhibitor				
	PI3K α	RLY-2608				
	FGFR2	Lirafugratinib (RLY-4008)				

DYNAMO® PLATFORM | 5 unnamed research programs

Anticipated 2025 Corporate Objectives

Breast Cancer
RLY-2608

- 2L pivotal trial start – 2025
- Full Ph1-2 data – 2025

Vascular Malformations
RLY-2608

- Clinical start – 1Q 2025

Fabry Disease
Pre-clinical

- Clinical start – 2H 2025

NRAS
Pre-clinical

- Clinical start – 2H 2025

Significant Capital to Achieve Goals

~\$840M
Cash as of the end of 3Q 2024

Expected to fund
current operating plan
into 2H 2027



DYNAMO® PLATFORM | 5 unnamed research programs



