OnKure Therapeutics

March 2026

Legends

This presentation contains forward-looking statements that involve substantial risks and uncertainties of OnKure Therapeutics, Inc. ("OnKure" or the "Company"). All statements other than statements of historical facts contained in this presentation, including statements regarding our future financial condition, results of operations, business strategy and plans, and objectives of management for future operations, as well as statements regarding industry trends, are forward-looking statements. Such forward-looking statements include, among other things, statements regarding the potential of, and expectations regarding, OnKure's product candidates and programs, including OKI-219 and the pan-mutant programs; the potential of PI3KaMUT inhibitor-based therapies; OnKure's ability to advance additional programs; the expected milestones and timing of such milestones, including additional data for OKI-219 from the PIKture-01 trial, details on the pan-mutant program and the timing of the submission of the IND applications for OKI 345 and OKI 355; the completion and expected timing of the closing and gross proceeds received by OnKure in the private placement; OnKure's expected use of net proceeds from the private placement, OnKure's expected cash runway, OnKure's ability to leverage insights from the PIKture-01 trial and statements regarding OnKure's financial position, including its cash runway. In some cases, you can identify forward-looking statements by terminology such as "estimate," "intend," " expect," "may," "plan," "potentially," "will" or the negative of these terms or other similar expressions.

We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: the risk that the conditions to the closing of the private placement are not satisfied; OnKure's limited operating history; the significant net losses incurred since inception; the ability to raise additional capital to finance operations; the risk that actual uses of cash and cash equivalents differ from the assumptions underlying our expected cash runway; the ability to advance product candidates through preclinical and clinical development; the ability to obtain regulatory approval for, and ultimately commercialize, OnKure's product candidates; the outcome of preclinical testing and early clinical trials for OnKure's product candidates, including the ability of those trials to satisfy relevant governmental or regulatory requirements and the potential that the outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials; OnKure's limited resources; the risk of adverse events, toxicities or other undesirable side effects; potential delays or difficulties in the enrollment or maintenance of patients in clinical trials; the decision to develop or seek strategic collaborations to develop OnKure's current or future product candidates in combination with other therapies and the cost of combination therapies; OnKure's limited experience in designing clinical trials and lack of experience in conducting clinical trials; the substantial competition OnKure faces in discovering, developing, or commercializing products; the ability to attract, hire, and retain highly skilled executive officers and employees; the ability of OnKure to protect its intellectual property and proprietary technologies; the scope of any patent protection OnKure obtains or the loss of any of OnKure's patent protection; developments relating to OnKure's competitors and its industry, including competing product candidates and therapies; reliance on third parties, contract manufacturers, and contract research organizations; legislative, regulatory, political and economic developments and general market conditions; and other risks. Information regarding the foregoing and additional risks may be found in the section titled "Risk Factors" in documents that OnKure files from time to time with the Securities and Exchange Commission. These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

OnKure is Developing a Differentiated Portfolio

OnKure Therapeutics

- **PI3Kα PAN-mutant inhibitors** with the highest known selectivity on helical and kinase mutations
- Distinct programs and compounds designed for **Vascular Anomalies** and **Cancer**
- An experienced R&D team to support portfolio expansion in vascular anomalies
- OnKure is not pursuing further clinical development of OKI-219 independently at this time; mature data to be presented in 2026
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Vascular Anomalies

OKI-355

- PI3Kα PAN-mut-selective inhibitor
- Best-in-class drug properties
- ~$7-10B+ US TAM[2]
- IND expected 1H 2027

Breast Cancer

OKI-345

- PI3Kα PAN-mut-selective inhibitor
- Best-in-class drug properties
- ~$9B+ US TAM 1L MBC[2]
- IND expected 1H 2027

[1] Financing announced March 27, 2026 expected to close on March 31, 2026, [2]US Total Addressable Market (TAM) based on market benchmarks and internal analysis

Led by a Team with Proven Experience

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Chief Executive Officer

ARRAY BIOPHARMA · BEND RESEARCH · Pfizer

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Infinity · agios · Genentech A Member of the Roche Group

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Pfizer · ARRAY BIOPHARMA · MERCK · Genentech A Member of the Roche Group

OnKure® THERAPEUTICS

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Pfizer · BEND RESEARCH

Qian Zhao, Ph.D.
VP and Distinguished Fellow

NOVARTIS · Pfizer · ARRAY BIOPHARMA

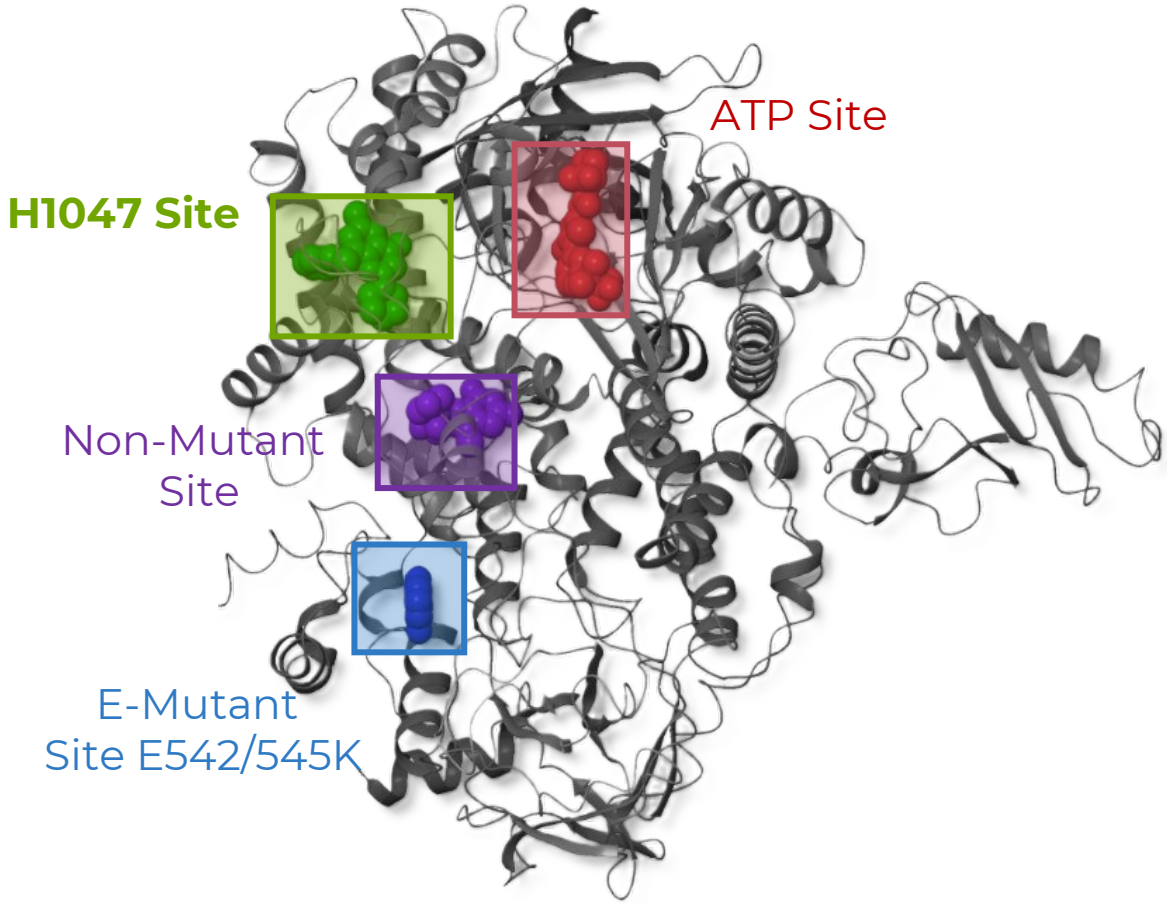
A Differentiated PI3Kα PAN Mutant Selective Portfolio

Program/Target	Initial Indication	Discovery	Preclinical	Clinical	Program Status	Next Anticipated Milestone
OKI-355 **PI3Kα^{PAN}** mutant-selective inhibitor	Vascular Anomalies				IND-Enabling Studies Ongoing	IND (1H 2027)
OKI-345 **PI3Kα^{PAN}** mutant-selective inhibitor	Breast Cancer				IND-Enabling Studies Ongoing	IND (1H 2027)

OnKure's Structure-Based Drug Design Enables Discovery of Allosteric Pan-Mutant PI3Kα Inhibitors

OnKure's Next-Gen Pan-Mutant PI3Kα Inhibitors

- OnKure's inhibitor design targets PI3Kα mutations at the **H1047 mutant site**
- Inhibitors affect key regulatory domains involved in activation of mutant PI3Kα
- Allosteric approach inhibits kinase and helical domain mutants (H1047X, E542K, and E545K)
- Selective to mutant PI3Kα vs. wild-type (wt)
- Potential to address on-target drug resistance from prior therapies targeting the ATP site and the non-mutant site



OnKure's Target Product Profile PI3Kα PAN Inhibitors

- ***Selectivity:*** Best-in-class with ~10X or greater cellular selectivity in cell lines with major hotspot mutations in PI3Kα
- ***Efficacy:*** Best-in-class anti-tumor activity in models of PI3Kα mutant HR+ BC and in models of PI3Kα mutant of VM (tumor regressions with single agent and in combination)
- ***Safety:*** Best-in-class avoidance of wild-type PI3Kα and sparing of associated toxicities (>10X selectivity translates to wider therapeutic index against toxicities associated with inhibition of WT PI3Kα)
- ***High target coverage*:** Ensures potential for deep and durable responses in PI3Kα mutant diseases (established target coverage required for single and combination activity)
- ***Combinable with current standards of care:*** Minimal drug-drug interaction risk ensures a broad range of combination strategies and the ability to move into adjuvant settings; avoidance of QTc prolongation
- ***Active against on-target resistance mutants:*** Captures patients that relapse on prior PI3Kα inhibitors
- ***Diverse IP estate*:** Protects assets and disables competition

Comparison of cellular selectivity of OnKure vs. competitor pan-mutant PI3Kα inhibitors

	PI3Kα Mutation		
Compound	**H1047R**	**E545K**	**E542K**
Alpelisib[2,3]	<1x	<1x	<1x
STX-478[2]	9x	1x	nr
RLY-2608[3]	4x	<1x	<1x
OKI-345[1]	**58x**	**18x**	**10x**
OKI-355[1]	**106x**	**24x**	**10x**

[1]Cellular selectivity values based on inhibition of pAKT determined by OnKure. Cellular potency for each compound was determined in cell lines with specific PI3Kα mutations shown in parentheses, T47D (H1047R), MCF7 (E545K), BT483 (E542K). Selectivity was derived from the ratio of the potency in wild-type PI3Kα SKBR3 cell line to the mutant cell lines. Reported values were determined from the selectivity derived from SKBR3 cells to mutant cells reported in [2]Buckbinder et al Cancer Discov 2023;13:2432–47 suppl., (nr = not reported) and [3]Varkaris et al Cancer Discov 2024;14:1–18, suppl. All values were rounded to the nearest whole number, or if the ratio was less than 1.0, <1.0 was used.

Vascular Anomalies Patients Deserve Precision Therapies

Vascular anomalies are heterogeneous and cause measurable functional impairment and burden

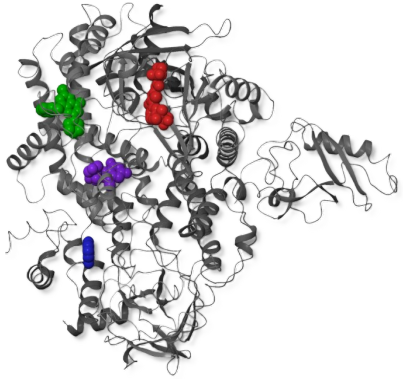
86K

Target PI3KCAm Patient Population in the US

Non-selective PI3Kα drugs are of limited use due to wild type toxicities

Mutant-selective PI3Kα drugs could transform standard of care and offer a lifetime of benefit

PI3Kα is a **clinically validated Vascular Anomalies target**



OKI-355 – PI3Kα pan-mutant selective candidate; IND 1H 2027

Our **approach restores cellular homeostasis** by selectively targeting mutant PI3Kα

OnKure's edge

Track record	R&D team experienced in rare diseases
IP	Ability to leverage existing OnKure IP
Target	Leading expertise in PI3Kα drug discovery
Clinical	Novel biomarkers + meaningful endpoints

Note: Prevalence based market benchmarks and internal analysis

Available Therapies for Vascular Anomalies are Inadequate

Alpelisib & Rapamycin Validate PI3Kα as Target, but Wildtype Toxicity Limits Activity

ALPELISIB (VIJOICE)

- **Weak foundation** for accelerated approval in PROS subset based on small, retrospective study
- **Failed EPIK-P2 confirmatory study** due to limited efficacy (ORR: 11% adults, 9% peds)[1] at lower doses to mitigate toxicity
- Ongoing EPIK-P4 study attempts to re-capture efficacy in PROS, again **pushing higher doses**
- EPIK-L1 explores expansion in LM despite **dosing uncertainties with poor target coverage** limited by wild-type toxicity
- **Trial endpoints lack clinical relevance** and no long-term data to support maintenance therapy

SIROLIMUS (RAPAMYCIN)

- **Not approved** in any subset of vascular malformations; off-label use
- Non-selective profile associated with **challenging toxicity profile including immunosuppression**
- Requires frequent **monitoring with blood tests** for dose control and safety surveillance:
  - **Blood** → myelosuppression (anemia, thrombocytopenia, leukopenia)
  - **Lipids** → hypercholesterolemia/ hypertriglyceridemia
  - **Kidneys and Liver** → creatinine changes, proteinuria, hepatic effects

[1]Canaud, G. et al. Epik-P2: A Phase 2 Study of Alpelisib (ALP) in Pediatric and Adult Patients (pts) with PIK3CA-Related Overgrowth Spectrum (PROS). Blood 144, 5512–5512 (2024)

Target Population: 86,000 U.S. Patients (PI3KCAm)

Multi-Billion-Dollar Opportunity, Significant Patient Burden, and Inadequate Treatment Options

Vascular Anomalies

Prevalence (U.S.)[1]	Approved Therapies	Disease Presentation
Venous Malformations **~ 22,000 PIK3CAm**	**None**	**Neurologic** Seizures, cognitive delays **Infection** Cellulitis, bacteremia **Organ abnormalities** Pulmonary, cardiac, renal, hepatic, GI **Functional impairment** Pain, muscular, orthopedic, soft tissue overgrowth **Lymphatic** Lymphedema, lesions, chylous effusion/ascites **Coagulopathies** Hemorrhage, thrombophilia **Psychologic** Anxiety, depression
Lymphatic Malformations **~49,000 PIK3CAm**	**None**	
PIK3CA Related Overgrowth Spectrum (PROS) **~ 15,000 PIK3CAm**	**Alpelisib** (approved in subset of PROS with severe disease manifestations)	

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[1]Prevalence and market size estimates based on market benchmarks and internal analysis

PIK3CA Mutated MBC Represents A Major Market Opportunity

A Multi-Billion-Dollar Market Opportunity

~38% of breast cancers harbor PIK3CA mutations[1]

Patient Population	Target Population (U.S. Patient Incidence)[2]	Total Addressable Market (TAM)[2]
1L HR+/HER2- mBC Estrogen Sensitive	**10,900**	**~$7-9B**
1L HR+/HER2- mBC Estrogen Resistant	**5,300**	**~$2-3B**
HR+/HER2- mBC 2nd-3rd Line	**9,750**	**~$2-3B**

OnKure's Differentiation

Best-in-Class
Safety and Tolerability

Enable Combinability
with Backbone Therapies
Across All Lines of Therapy

Activity and Tolerability Drive
Extended Duration of Therapy

[1]Third party source. [2] Total Addressable Market (TAM) and target patient population based on market benchmarks and internal analysis.

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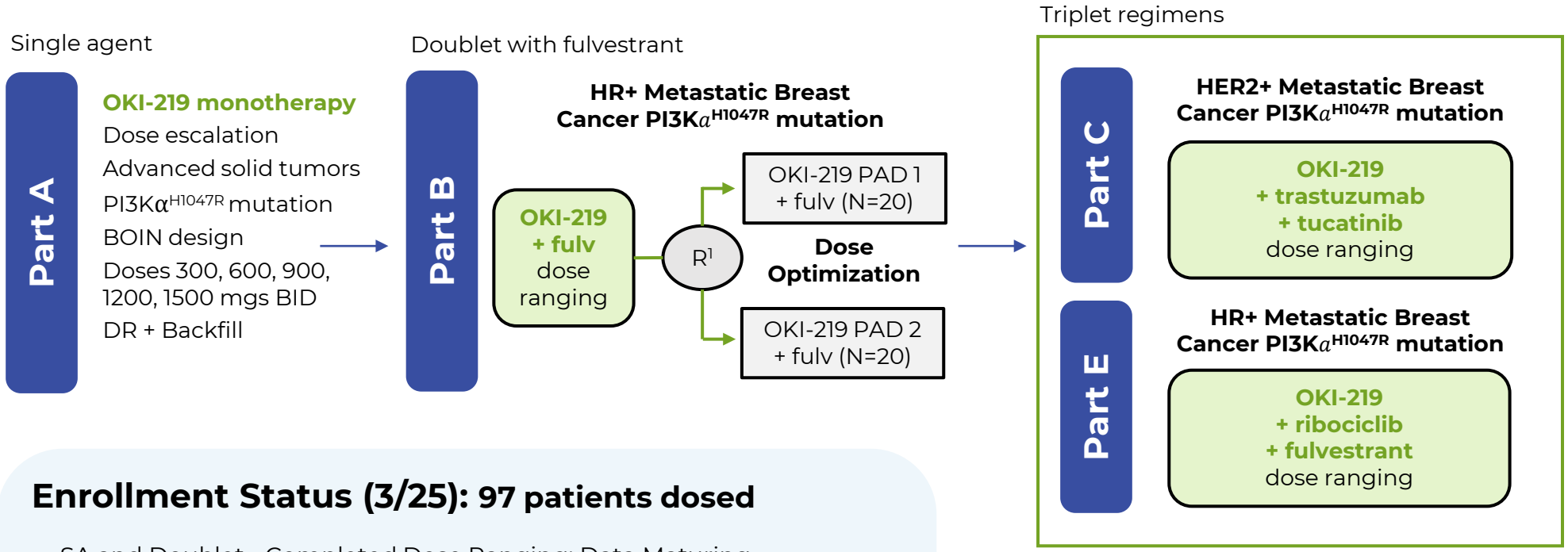
OKI-219 – PIKture-01 Trial Design and Status

Completing Dose Selection in CDK-based Triplet Combination



Enrollment Status (3/25): 97 patients dosed

- SA and Doublet - Completed Dose Ranging; Data Maturing
  - **Part A** Monotherapy: 38 patients – last patient dosed Sep '25
  - **Part B** Fulv combination: 33 patients[1] – last patient dosed Jul '25
- Triplets – Parts C and E – Enrollment Nearly Complete
  - **Part C** + Trastuzumab + Tucatinib: 6 patients dosed
  - **Part D** + Atirmociclib + Fulvestrant: not initiated
  - **Part E** + Ribociclib + Fulvestrant: 20 patients dosed

Key Eligibility Criteria:

- **Prior PI3K inhibitors of any kind allowed**
- **Treated or untreated asymptomatic brain metastasis allowed**
- **HbA1C < 8% allowed**

Key Endpoints:

- Safety and tolerability
- PK, PD, RP2D incorporating Project Optimus
- Anti-tumor activity assessed by ORR by RECIST v1.1, DOR, PFS
- Patient reported outcomes via EORTC QLQ-C30 score during dose optimization/exp only

Abbreviations BOIN: Bayesian Optimal Interval Design; DOR: Duration of Response; ORR: Objective Response Rate; PFS: Progression Free Survival; PAD: Pharmacologically Active Dose; PD: Pharmacodynamics, PK: Pharmacokinetics; R: Randomization; RP2D: Recommended Phase 2 Dose; SOC: Standard of Care. PIKture-01 trial (NCT:06239467). (1) includes one cross over patient.

OKI-219 Clinical Progress to Date

OKI-219 Demonstrated Activity and Safety in Doublet and Triplet Combinations. Mature Data on all Cohorts will be Presented in 2026.

OKI-219 Single Agent and Fulvestrant Doublet

- Demonstrated activity and safety in heavily pre-treated patients
- No significant PI3K wild type toxicities observed at any dose level in single agent and doublet combination – The majority of all adverse events are grade 1 and 2
- Clinical activity observed in PI3K pathway inhibitor naïve patients, ~30% ORR in this subset of patients at 600 mg BID and higher
- Single agent and doublet data supported triplet expansion in HER2+ and HR+ ABC

OKI-219+ Ribociclib + Fulvestrant HR+ ABC Trastuzuamb + Tucatinib HER2+ ABC

- Only known PI3K inhibitor to combine with full dose ribociclib without significant AEs
- Completing dose selection for late-stage development in CDK based triplet
- No significant PI3K wild type toxicities observed at any dose level in triplet combinations
- Clinical activity observed in both HER2+ triplet and HR+ triplet ABC patients
- Responses observed in HR+ patients with prior progression on both PI3K pathway and CDK inhibitors

Financial Overview

Stock Symbol	NASDAQ: OKUR
Cash and Investments	**$59 million** cash and cash equivalents as of December 31, 2025 **$150 million** in expected gross proceeds from the financing[1]
Cash Runway	Cash and cash equivalents expected to provided **runway into 2029**
Common Stock	**13.7 million shares** of common stock outstanding as of Dec 31, 2025 **26.7 million shares** of common stock and pre-funded warrants to purchase **9.4 million shares** of common stock expected to be issued in conjunction with the financing[1]

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