

NASDAQ: EPIX

ESSA

ESSA CORPORATE PRESENTATION JANUARY 2023

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Focused on the development of novel therapies for the treatment of prostate and other androgendriven cancers

Company

- Experienced management team with deep expertise in oncology and drug development
- Headquartered in South San Francisco and Vancouver

Technology & Products

- Lead candidate **EPI-7386** is a first-in-class oral, small molecule androgen receptor N-terminal domain inhibitor ("Aniten")
- EPI-7386 is being developed as both a monotherapy in late-stage metastatic castrationresistant prostate cancer and in combination with antiandrogens in 1st line mCRPC
- Initial clinical data show EPI-7386 is well-tolerated as a monotherapy and in combination with leading antiandrogens; early combination data with enzalutamide showed 4/6 patients achieving a PSA90 in 90 days
- First generation AR NTD protein degrader (ANITAC) in preclinical development

Financial Details

- Listed on NASDAQ (EPIX)
- Cash and short-term deposits: \$167.2M (September 30, 2022); runway through 2025

Experienced Management Team



David R. Parkinson, MD *President & Chief Executive Officer*



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NH) NATIONAL CANCER INSTITUTE



nodality



Peter Virsik, MS, MBA EVP & Chief Operating Officer





David S. Wood, MBA, CPA, CMA Chief Financial Officer







Alessandra Cesano, MD Chief Medical Officer

nanoString







CLEAVE

THERAPEUTICS

PUBLIC HEALTH PROBLEM	LARGE MARKET	VALIDATED THERAPEUTIC TARGET	NEED FOR NEW THERAPEUTIC STRATEGIES
 Prostate cancer is the 2nd most common cause of male cancer deaths American Cancer Society estimates 268,000 new cases and 34,500 deaths in 2022¹ 	 Over \$8.6B in global sales generated in 2021 by leading antiandrogens² Newest antiandrogens: Zytiga® (abiraterone acetate), Xtandi® (enzalutamide), Erleada® (apalutamide) and Nubeqa® (darolutamide)² 	 Androgen receptor (AR) signaling is critical for prostate cancer development and progression^{3,4,5} Mounting evidence that progression to CRPC remains dependent upon persistent AR signaling driven by AR resistance mechanisms^{3,5} 	 Resistance to second- generation antiandrogens is common and on average occurs within a year of starting therapy⁶ Clinical results suggest that more potent AR inhibition used earlier in therapy may provide improved clinical outcomes for patients⁷

 American Cancer Society. (2022). Key Statistics for Prostate Cancer. Retrieved from https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html.
 2021 financial reports from www.sec.gov. Robinson D, et al. Cell, 2015.
 Chen CD, et al. Nat Med, 2004.
 Kumar A, et al. Nat Med, 2016.

6. Sharp A, et al. JCl, 2019. 7. ESMO 2021.

Large Opportunity in U.S. Prostate Cancer Market *



• Sher, H, et al. PLOS One, 2015. 3LmCRPC patients are estimated as the yearly mortality incidence due to prostate cancer.

Prostate Cancer Evolution and AR Dependency



PTEN-PI3K-AKT, Wnt, neuroendocrine, other tumor growth drivers





EPI-7386, First-in-Class NTD AR Inhibitor

EPI-7386's Novel MoA Uniquely Inhibits the NTD of the Androgen Receptor, Potentially Overcoming Resistance to Standard-of-Care

- All current antiandrogens function through the ligandbinding domain (LBD) of the androgen receptor (AR)
 - Known antiandrogen resistance mechanisms develop at the LBD
- EPI-7386 specifically binds to the N-terminal domain (NTD) of the AR, a region of the androgen receptor required for AR activity
- As a result of this binding, EPI-7386 is active against multiple AR forms, including those resistant to current antiandrogens
- EPI-7386's novel method of inhibiting the AR may lead to greater AR suppression when used in combination with current antiandrogen therapies



Granted unique USAN drug stem of "Aniten" as a AR NTD inhibitor

Hong NH, et al. AACR-NCI-EORTC-Virtual Int Conf, 2021.
 De Mol E, et al. ACS Chem Biol, 2016.

3. Andersen RJ, et al. Cancer Cell, 2010. 4. De Mol E, et al. ACS Chem Biol, 2016. 5. Yang YC, et al. Clin Cancer Res, 2016.



EPI-7386	Target Criteria	Description
\checkmark	Potency	In vitro potency in the range of second-generation antiandrogens
\checkmark	Activity	In vivo xenograft anti-tumor activity in both antiandrogen-sensitive & resistant models
\checkmark	ADME/PK	Low <i>in vitro</i> metabolism, good animal ADME & human $t_{1/2} \sim 24$ hrs
 ✓ 	Safety	Specific NTD on-target activity, minimal off-target binding, clean toxicology profile
\checkmark	DDI	Appropriate properties to combine with other drugs (e.g. drug-drug interactions (DDI), etc.)
\checkmark	СМС	Simple synthesis of drug substance and favorable pharmaceutical properties for the drug product

EPI-7386 Monotherapy Clinical Development for AR-Driven CRPC



EPI-7386 Phase 1 Monotherapy Study in mCRPC Patients: Study Design

- First-in-human Phase 1 multi-center open-label study enrolling mCRPC patients failing standard-of-care therapy
- Two-part study: Phase 1a dose-escalation followed by Phase 1b dose expansion



- No limitations on the # prior lines of therapy
- Visceral metastases permitted
- Prior chemotherapy permitted



Patients Enrolled Under the QD Dosing Regimen were Heavily Pretreated and Clinically/Molecularly Complex

Parameter	QD (n = 31)	ctDNA% 40	
Median age (range), yrs	72 (50-85) yrs	20 0 17P53 22 22 22 22 22 22 22 22 22 22 22 22 22	
Median # lines of prior therapy (range)	7 (4-13)	Cell CDK4 CDK6 CDK04 CDKN2A CDKN1B	
Median # lines of prior therapy for mCRPC (range)	4 (2-10)	PISC PIK3CB	Copy Nu Ampli Gain Delet Deep
 Type of prior therapy, n (%) Abiraterone ("ABI") Enzalutamide ("ENZ") Both (ABI + ENZ) Darolutamide/Apalutamide Chemotherapy 	 27 (87.1%) 25 (80.6%) 22 (71%) 4 (12.9%) 18 (58.1%) 	WNT arrows are arrows arrows are arrows arrows are arrows arrows are arrows arrows are a	Structura Ves No Mutations Fram Stopg Non-1 Splice
Median baseline PSA, (range), ng/ml	94.5 (5.4-1900)	FOXP1	
Median baseline PSA doubling time (range), months	2.1 (0.85 -9.5)	SPOP Other NKX3-1 ZFHX3	
Median baseline ctDNA* % (range)	29% (4-73%)	Molecular Alteration	Froquency (n=20)
Visceral Disease, n (%)	9 (29%)	AR-associated	Requency (n=29)
NSE** > 10 ng/ml, n (%)	9 (29%)	Non-AR-associated	93% FS

TRAE* Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3** n (%)	Total n (%)
Anemia	4 (10.2)	2 (5.1)	1 (2.5)	7 (17.9)
Aspartate aminotransferase increased	2 (5.1)	0 (0)	0 (0)	2 (5.1)
Diarrhea	3 (7.7)	2 (5.1)	0 (0)	5 (12.8)
Fatigue	1 (2.5)	5 (12.8)	0 (0)	6 (15.4)
Hot Flush	0 (0)	4 (10.2)	0 (0)	4 (10.2)
Nausea	6 (15.4)	1 (2.5)	0 (0)	7 (17.9)

- All TRAEs (exception of one occurrence of what was later considered non-related Grade 3 anemia) were Grade 1 and 2
- No apparent dosedependency was observed
- All the Grade 2 TRAEs of diarrhea occurred at doses ≥ 600 mg QD
- Low dose-reduction rate (8.1%) due to related AEs (5 cases of Grade 2 diarrhea in 2 subjects)

*Treatment Related Adverse Event ("TRAE")

**Initially, principal investigator considered Grade 3 anemia in a patient who received 400 mg BID EPI-7386 as "possibly related" (due to antiandrogen safety profile) although confounded by concurrent rapid bone disease progression (ALP>1,000); later changed to "unlikely related"

EPI-7386 Exposures Reached the Predicted Efficacious Thresholds Observed in Preclinical Enzalutamide-Resistant Models

- EPI-7386 has a long half life (>24hrs) which supports QD administration
- The steady state AUC EPI-7386 exposure increases with higher doses
- All doses reached exposures above the minimum target drug threshold
- Doses > 400mg per day of EPI-7386 exhibit AUC concentrations generally above the highest target drug threshold
- The 600 mg QD cohort exhibited the highest AUC
- BID dosing allows for higher C_{min} drug levels

EPI-7386 C1D28 AUC Across Doses



Longer Duration of Treatment on EPI-7386 is Associated with Less Prior Therapy for mCRPC

QD Dosing Regimen Patients

- ~ 30% of patients across all dose levels remained on therapy longer than 3 months
- The patients who progressed before or at 12 weeks had in general: >10 ng/mL NSE, prior chemotherapy, visceral metastases and received >3 lines of therapy for mCRPC
- One patients was treated for 18 months; one patient is currently on study at 1000 mg QD in cycle 17
- No obvious dose response observed

BID Dosing Regimen Patients

- ~60% of patients across the two dose levels remained on therapy longer than 3 months
- One patient remains on therapy



PSA Reductions were Observed in a Clinically Defined Subset of Patients

PSA decrease or PSA stabilization was observed in patients with:

- No visceral disease
- Fewer DNA genomic aberrations in non-AR oncogenic pathways
- < 3 lines of therapy





Phase 1a QD Dosing Regimen: % ctDNA Decreases Suggest Activity Against AR-Driven Tumors

In 17 patients with measurable ctDNA levels at baseline:

- ctDNA declines were observed in patients harboring AR point mutations, AR gain/amplification and AR truncations
- No clear dose response observed for the % ctDNA decrease at week 12
- % ctDNA decreases were observed even in patients whose PSA levels were increasing

According to FDA draft guidance pertaining to the early-stage solid tumor setting, "... ctDNA could be used in early phase clinical trials to aid in signal finding of drug activity and to potentially aid sponsors in their drug development plans."*



Case 1 from QD Dosing Regimen: Progressive, Deep and Durable PSA Decrease and Mixed Radiographic Tumor Response

Baseline Parameter	
Age (years)	79
PC Dx date	08/2014
mCRPC Dx	06/2017
Prior Rx for mCRPC	Enzalutamide Provenge Abiraterone
Metastatic sites	Bone, nodal
dtPSA* (m)	4
СТС	0
ctDNA %	0
Tumor Burden (mm)	59
NSE (ng/ml)	< 5 ng/mL
AR-related alterations	None
Non-AR alterations	None



Radiographic 20% decrease in target lesions at week 36

- 200 mg/dose QD AUC_{C1D28} = 95,500 hr*ng/mL
- Patient received 18 cycles of single-agent EPI-7386 with progressively escalating dose levels from 200 mg to 1000 mg QD

Mixed response by AIQ platform





EPI-7386 Monotherapy Phase 1a: Key Findings

Key safety results and pharmacokinetic data from both QD and BID patients as of June 1, 2022:

- EPI-7386 was safe and well-tolerated at all dose levels and schedules tested, with no dose-limiting toxicities and only Grade 1 and Grade 2 adverse events
- EPI-7386 has a long half life (>24hrs) and steady state AUC EPI-7386 exposures increase with higher doses; all doses reached exposures above the minimum target drug threshold

Key response findings in both QD and BID patients as of June 1, 2022:

- Tumor volume decreased in five patients who had measurable disease and were on therapy for more than 12 weeks
- In 17 patients with measurable ctDNA levels at baseline, ctDNA declines were observed in patients harboring AR
 point mutations, AR gain/amplification and AR truncations, suggesting EPI-7386's potential activity against these
 tumors
- PSA decreased or PSA stabilized in a clinical subset of patients: no visceral disease, fewer DNA genomic aberrations in non-AR oncogenic pathways, and fewer than 3 lines of therapy
 - Provides further information to refine the monotherapy development program patient population

Phase 1b Dose Expansion is ongoing and testing 2 doses/schedules of single agent EPI-7386 in a less heavily pretreated mCRPC patient population (i.e., chemotherapy naive, post-second-generation antiandrogens)

Next Steps in the EPI-7386 Phase 1 Monotherapy Study

- Verify the recommended Phase 2 dose 600mg BID or 600 mg QD
- Understand late stage mCRPC patient biology and identify patients with AR-driven tumors
- Gain further insight of the biological activity of EPI-7386 in less heavily pretreated patients







EPI-7386 in Combination with Second Generation Antiandrogens

EPI-7386 Combination Study Clinical Program for AR-Driven CRPC



Preclinical Rationale for the Combination of EPI-7386 with Antiandrogens



Mouse VCaP Xenograft Efficacy



- Decades of clinical research link improved clinical results with deeper AR axis suppression
- Combining an AR NTD-inhibitor with an LBD-inhibitor provides two complementary ways of inhibiting AR biology
- Preclinical studies support deeper and broader suppression of ARdriven biology by combining EPI-7386 with antiandrogens

EPI-7386 Combination Development Program with Second-Generation Antiandrogens

Astellas	ESSA collaboration with Astellas to evaluate EPI-7386 in combination with Xtandi [®] (enzalutamide) in an ESSA-sponsored Phase 1/2 clinical study in mCRPC patients naïve to second generation antiandrogens (study began 1Q2022)
Janssen	Janssen collaboration with ESSA to evaluate EPI-7386 in combination with Erleada ® (apalutamide) and Zytiga ® (abiraterone acetate) + prednisone in a two arm Phase 1/2 clinical study in mCPRC patients naïve to second generation antiandrogens; initial data from three enrolled patients reported October 2022
BAYER	Bayer collaboration with ESSA to evaluate EPI-7386 in combination with Nubeqa [®] (darolutamide) in a Phase 1/2 clinical study in mCRPC patients
Investigator- Sponsored Neoadjuvant Study	A 12-week two-arm randomized study of Nubeqa vs. EPI-7386 + Nubeqa in PC patients undergoing prostatectomy for high risk localized prostate cancer

Phase 1/2 EPI-7386 plus Enzalutamide Combination Study Trial Design in mCRPC Patients Naïve to Second-Generation Antiandrogens

- Phase 1/2 multi-center open-label study enrolling mCRPC patients naïve to second-generation antiandrogens
- Two-part study: Phase 1 dose-equilibration followed by Phase 2 open-label randomized study



- Phase 1 study will focus on the PK and safety of EPI-7386 and enzalutamide when administered in combination along with establishing the RP2D for both drugs to address any possible drug-drug interactions
- Phase 2 study will assess the anti-tumor activity of the combination versus single agent enzalutamide at the standard of care dose

EPI-7386 and Xtandi (Enzalutamide) Phase 1/2 Combination Study Update: Initial Data from First Two Cohorts in Phase 1



Safety	 EPI-7386 and enzalutamide were well-tolerated with no DLTs, no Grade 3 drug-related AEs, and a safety profile consistent with second generation antiandrogens (e.g. grade 1 or 2 AEs of fatigue and hot-flashes)
Pharmacokinetics (PK)	 Enzalutamide exposure minimally impacted by EPI-7386 administration EPI-7386 exposure impacted by enzalutamide with lower exposures of EPI-7386 observed, as anticipated; 4 dose cohorts will be needed to determine the combination RP2D One patient was discontinued from the study after the DLT period due to a concomitant medication (strong CYP3A inducer) interaction with enzalutamide and EPI-7386 which resulted in a significant decrease in exposure to both drugs
Clinical Activity	 Rapid, deep and durable prostate specific antigen reductions observed 5 of 6 patients achieved a PSA90 regardless of prior chemotherapy status (data cutoff in Oct 2022) 4 of 6 patients achieved a PSA90 in 90 days

Prior Antiandrogen Pivotal Studies May Provide Insight into Translating Early Clinical Data into Potential Long-term Treatment Benefits

Best PSA90 Change at 90 Days from Historical Studies of mCRPC

Patient Population	Agent	PSA90 (90 Days)	Study Type	Patient Number	PSA90 (Overall)	Reference
mCRPC pre-chemo (PREVAIL)	ENZ	37%	Pivotal		47%	Beers et al., NEJM, 2014; Armstrong et al., Eu Assoc of Uro, 2020.
mCRPC pre-chemo (PREMISE)	ENZ		Observational	1171	45%	Payne et al., Int J of Canc, 2021.
mCRPC pre-chemo (COU-AA-302)	ABI	22%	Pivotal		31%	Ryan et al., NEJM, 2013; Xu et al., Clin Canc Rsch, 2015.
mCRPC pre-chemo (ACIS)	ABI		Pivotal		47%	Saad et al., Lancet Onc, 2021.
mCRPC pre-chemo (ACIS)	ABI+APA		Pivotal		53%	Saad et al., Lancet Onc, 2021.
mCRPC post-chemo (AFFIRM)	ENZ	13%	Pivotal		25%	Scher et al., NEJM, 2012; Armstrong et al., Cancer 2017.
mCRPC pre-chemo (PREMISE)	ENZ		Observational	418	31%	Payne et al., Int J of Canc, 2021.
mCRPC post-chemo (COU-AA-301)	ABI	13%	Pivotal		14%	Xu et al., Clin Canc Rsch, 2015.

In mCRPC patients on treatment with enzalutamide, the depth of the 13-week (90 day) PSA response correlates well with long-term treatment benefits and may provide an early guide to the long-term patient treatment benefits of combination treatment*

Longitudinal PSA Changes Under Treatment for Cohort One and Cohort Two Patients



- Deep and durable PSA responses observed in 5 of 6 evaluable patients
 - Prior chemotherapy did not appear to impact response rate
 - Enzalutamide exposures still less than full
- Rapid PSA declines with 4 of 6 patients achieving a PSA reduction of 90% ("PSA90") by 90 days
- Currently enrolling cohort 3 which is dosing 600mg BID EPI-7386 with 120mg enzalutamide
- Given the limited number of treated patients, no firm conclusions regarding the PSA reductions can be drawn but the data compare favorably to historical controls

EPI-7386 in Combination with Erleada and Zytiga: Phase 1/2 Clinical Update in First Three Enrolled Patients



Janssen treated three mCRPC patients (pre-chemotherapy) with the combination of EPI-7386 and Erleada[®] (apalutamide) and Zytiga[®] (abiraterone acetate) plus prednisone for up to four months of therapy

Safety	 In all three patients, the combination of both investigational drug products was safe and well tolerated
Pharmacokinetics (PK)	 In all three patients, the combination of both investigational drug products yielded sufficient exposures of each investigational drug product, indicative of pharmacological activity
Clinical Activity	 Initial clinical activity was observed in patients, with two of the three patients achieving a PSA90 within 90 days





Milestones and Cash Flow

ESSA Research and Development Pipeline



Discovery

PROGRAM	INDICATION	RESEARCH	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	COLLABORATIONS
3rd-Generation AR N-Terminal Domain Inhibitor	Prostate Cancer						
AR N-Terminal Domain Degrader ("ANITAC")	Prostate Cancer						
AR N-Terminal Domain Tau-1 Site Inhibitor	Prostate Cancer						

ESSA Upcoming Milestones

EPI-7386 Programs	Timing		
Monotherapy			
Present clinical update on Phase 1 trial	Completed		
Establish the recommended Phase 2 dose (RP2D)	Completed		
Initiate Phase 1b expansion study	Completed		
Complete enrollment into the Phase 1b expansion study	1H2023		
Combination			
Establish the RP2D for EPI-7386/enzalutamide combination trial	1H 2023		
Initiate Phase 2 portion of EPI-7386/enzalutamide combination trial	1H 2023		

Discovery	Timing
Initiate IND-enabling studies for an ANITAC NTD degrader	2023

Nasdaq: EPIX		
Cash	\$167.2M reported at September 30, 2022 (no debt O/S)	
Shares	\sim 47M (44M I/O common shares and 3M prefunded warrants)	
Covering Analysts	Bloom Burton - <i>David Martin</i> Jefferies - <i>Maury Raycroft</i> Oppenheimer - <i>Mark Breidenbach</i> Piper Sandler - <i>Joe Catanzaro</i>	

Current cash runway through 2025 funds:

- Completion of Phase 1 dose escalation & expansion monotherapy studies
- Completion of Phase 1/2 combination studies with antiandrogens
- Phase 2 monotherapy pivotal study
- Pipeline work including preclinical studies with Anitens in other AR-driven tumors



ESSA

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