A MEDICINE COMPANY

LILLY ONCOLOGY ASCO INVESTOR EVENT

JUNE 2, 2024

Lilly

Safe Harbor Provision

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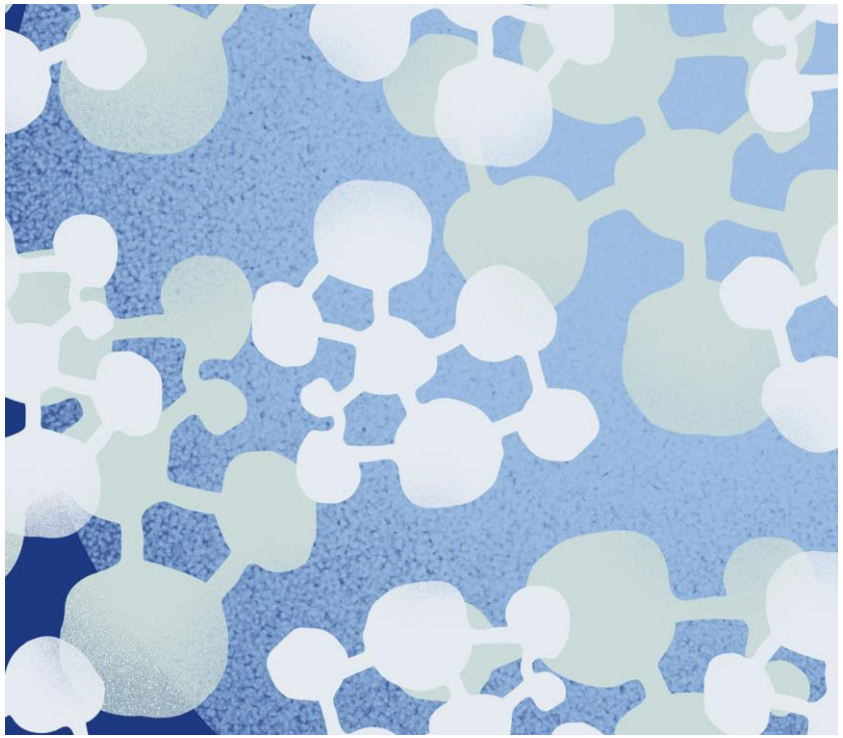
The company undertakes no duty to update forward-looking statements except as required by applicable law

Agenda



Introduction, Lilly Oncology R&D Turnaround and Commercial Performance

Jake Van Naarden, President

Lilly Oncology Portfolio

Lillian Smyth, M.D., Global Head, Breast Cancer
John Pagel, M.D., Ph.D., Global Head, Hematology
Geoff Oxnard, M.D., Global Head, Thoracic Cancer
Arjun Balar, M.D., Global Clinical Development
Barry Taylor, Ph.D., Chief Scientific Officer

Q&A Session

Lilly Oncology Leadership Team

Jake Van Naarden
President

Barry Taylor, Ph.D.
Chief Scientific Officer

Kara Clinton
Global Medical Affairs

Winselow Tucker
Chief Commercial Officer

Arjun Balar, M.D.
Global Clinical Development

Lillian Smyth, M.D.
Global Head, Breast Cancer

John Pagel, M.D., Ph.D.
Global Head, Hematology

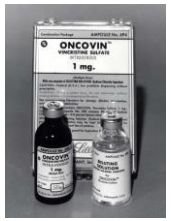
Geoff Oxnard, M.D.
Global Head, Thoracic Cancer

Oncology R&D Turnaround

Jake Van Naarden, President

Lilly's History in Oncology

CHEMOTHERAPY ERA



- **Oncovin®** and **Velban®** approved in **1960s**
- Still in use today

- **Gemzar®** approved in **1995**
- First active drug in pancreatic cancer

- **Alimta®** approved in **2004**
- Mainstay of chemo combinations, maintenance therapy, and backbone for IO

MONOCLONAL ANTIBODIES

- **Erbitux®** acquired as part of **2008** ImClone acquisition
- Among the first mAbs approved for use with solid tumors

- **Cyramza®** approved in **2014**
- Mainstay in post-KEYNOTE-189 lung cancer

TARGETED THERAPY

Verzenio™ abemaciclib

- **Verzenio®** first approved in **2017** for metastatic breast cancer
- First CDK4/6 inhibitor approved in early breast cancer

CDK = cyclin-dependent kinase; IO = immuno-oncology; mAb = monoclonal antibody.

Drug Development Approach at Lilly

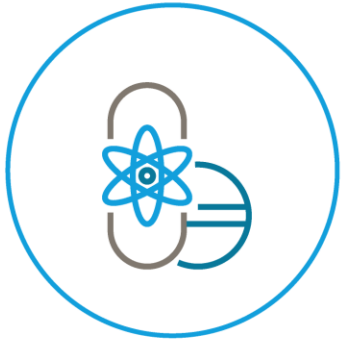
IDENTIFY
the right targets

Direct resources to high confidence areas of cancer biology

Choose targets with the greatest unmet need based on insights from:

- Clinicians
- Scientific Advisors
- Academic Researchers
- Patients

BUILD
the right medicines



Rationally design compounds that:

- Selectively inhibit the target
- Deeply inhibit the target
- Exhibit favorable medicinal properties

Employ varied discovery strategies:

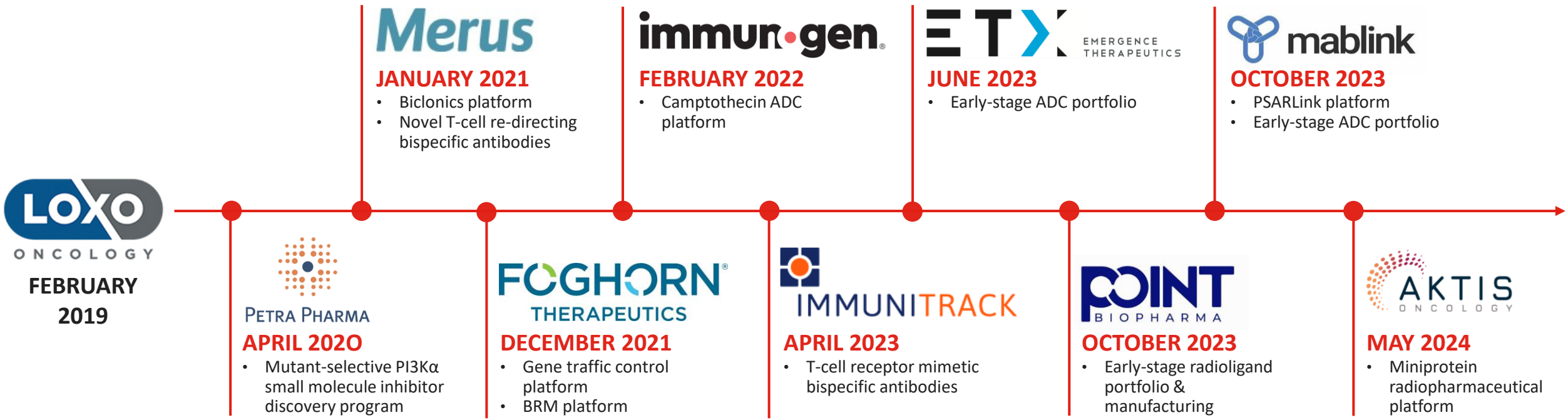
- In-house R&D
- In-licensing & Acquisitions
- Discovery Collaborations

STUDY
the right patients

Explore medicines in well-defined patient populations

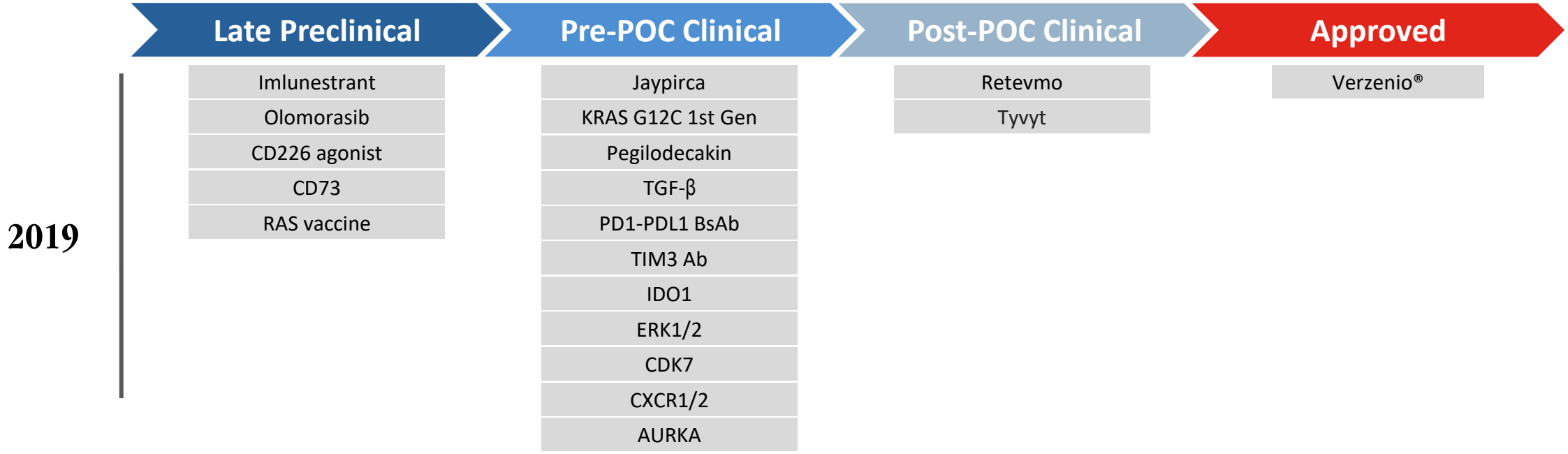
- Identify early response signals
- Accelerate development through novel clinical and regulatory strategies
- Engage key stakeholders throughout the process

External Innovation Focus After Loxo Acquisition

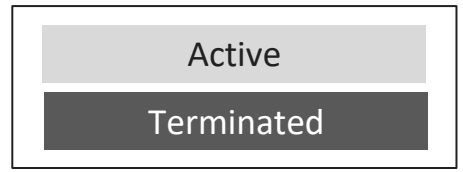


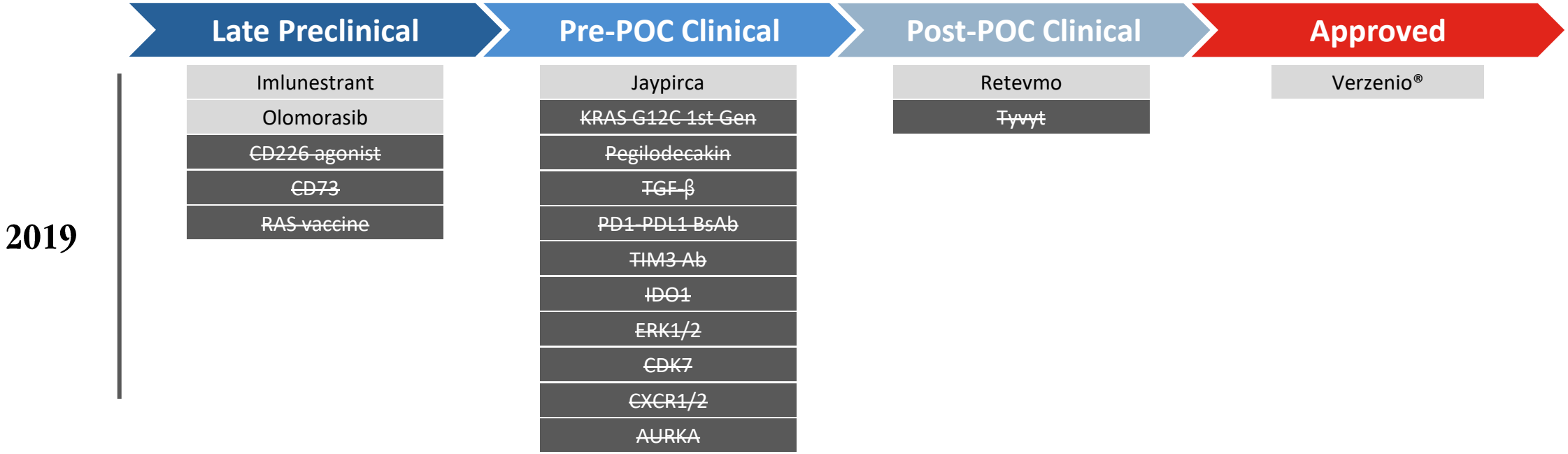
ADC = antibody drug conjugates.

Oncology R&D Turnaround Since 2019

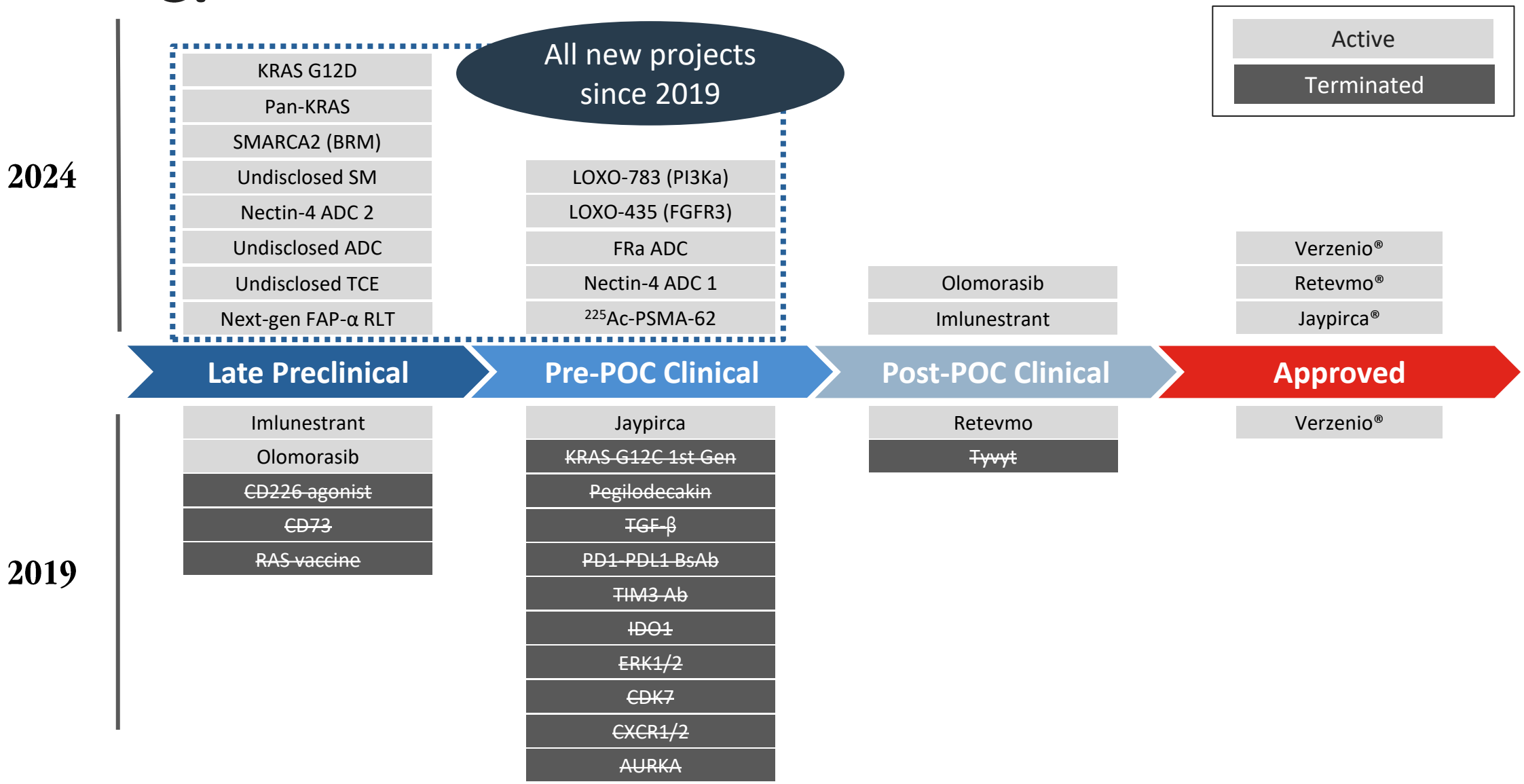


Oncology R&D Turnaround Since 2019

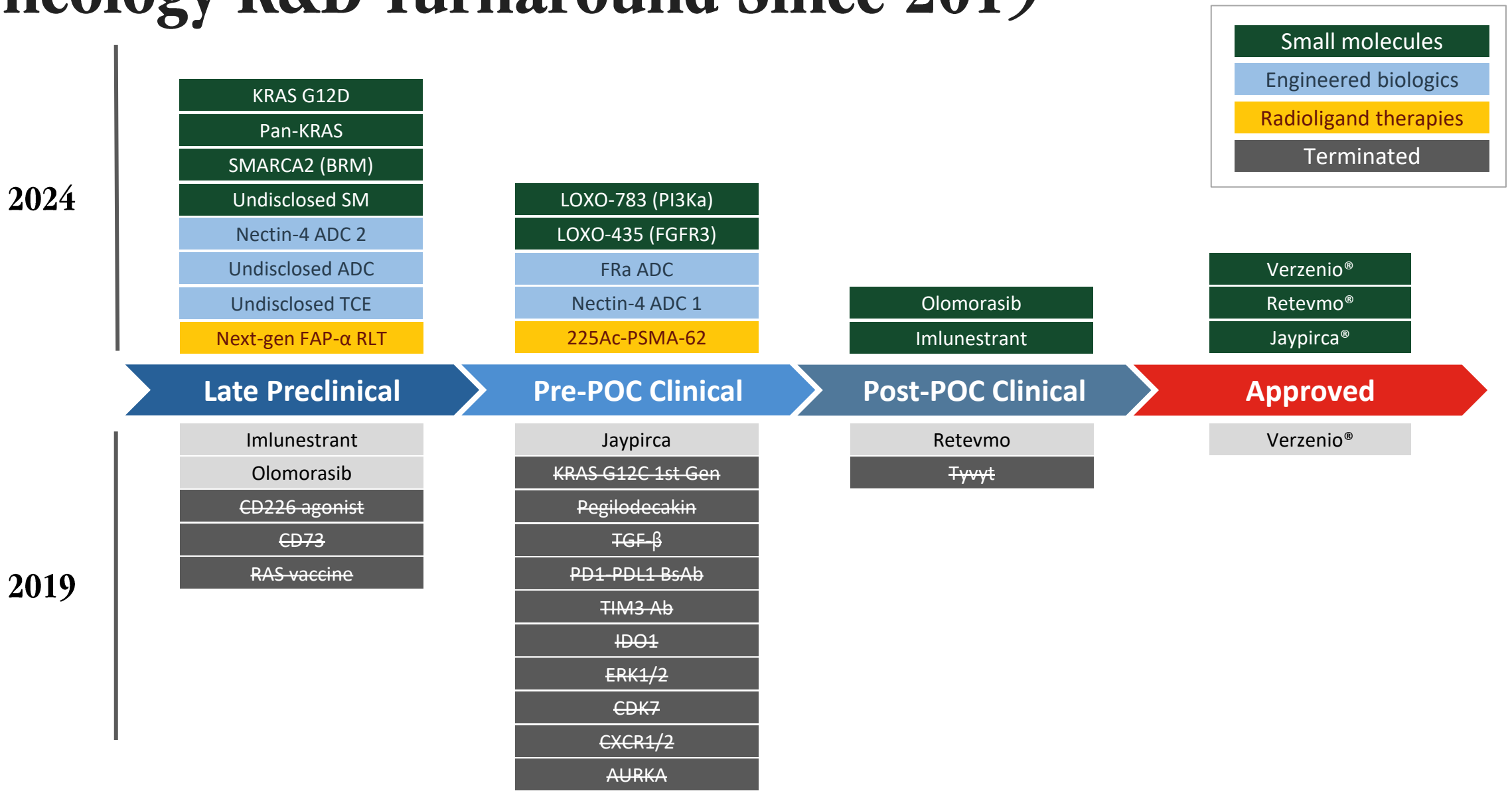




Oncology R&D Turnaround Since 2019



Oncology R&D Turnaround Since 2019



Portfolio Momentum

8 Pivotal Randomized Trial Readouts

Outcome	Medicine	Study	Readout Timing
✓	Retevmo®	LIBRETTO-431	Jul ‘23
✓	Retevmo®	LIBRETTO-531	Aug ‘23
✓	Verzenio®	MonarchE 5-year data	Aug ‘23
✗	Verzenio®	Monarch-3 Overall Survival	Aug ‘23
✓	Jaypirca®	BRUIN-CLL-321	Nov ‘23
✗	Verzenio®	CYCLONE-2/3	Feb ‘24
✓	Verzenio®	PostMonarch	Q2 ‘24
	Imlunestrant	EMBER-3	2H ‘24

Portfolio Momentum

Active First Human Dose (FHD) Agenda for 2024

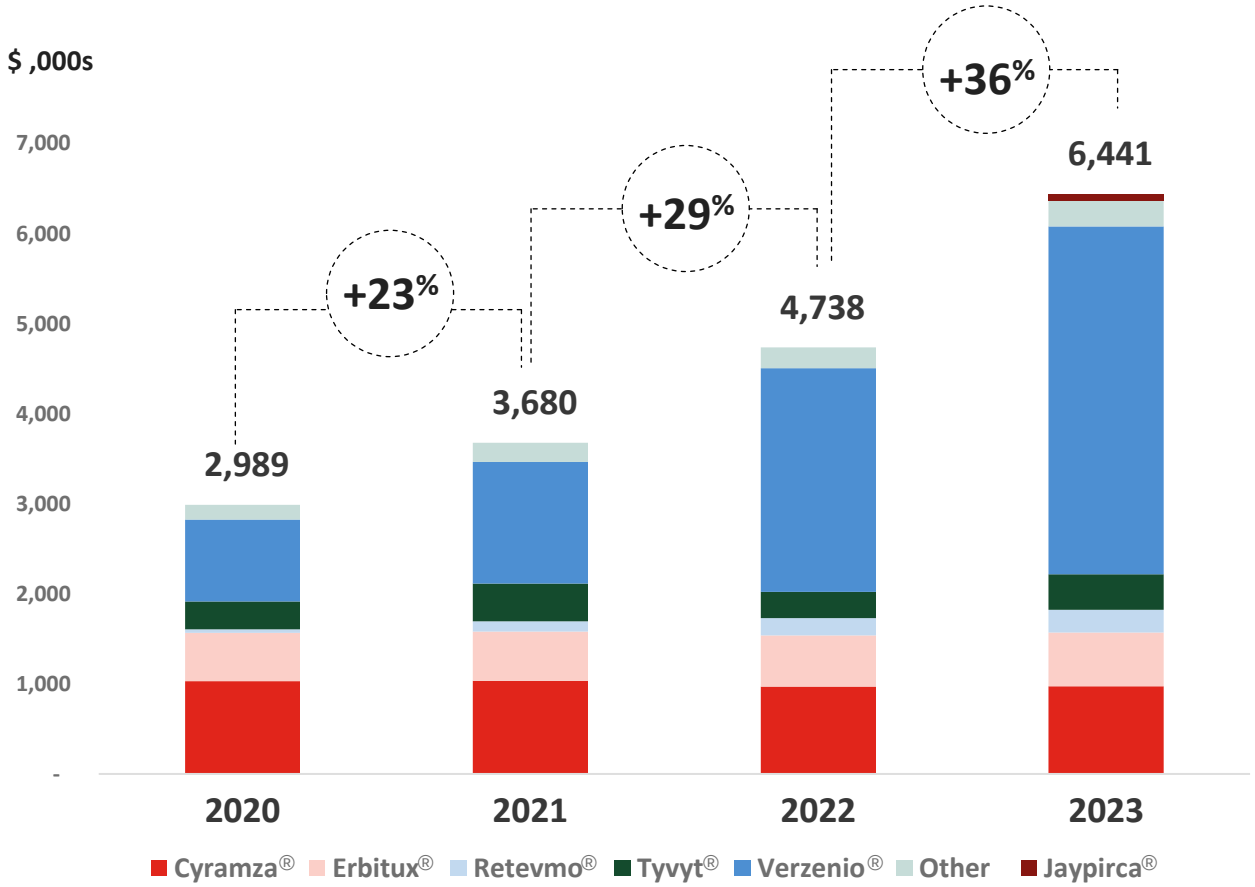
FHD Achieved	Target/Program	Patient Focus
✓	^{225}Ac-PSMA-62	Prostate cancer
✓	Nectin-4 ADC 1	Bladder cancer
	Nectin-4 ADC 2	Bladder cancer
✓	FRa ADC	Ovarian cancer
	SMARCA2 (BRM) Inhibitor	Non-small cell lung cancer (BRG1 loss)
	KRAS G12D	Pancreatic cancer, Colorectal cancer, Non-small cell lung cancer
	Pan-KRAS	Pancreatic cancer, Colorectal cancer, Non-small cell lung cancer
	Next-Gen FAPi RLT	Multiple solid tumors

Oncology Commercial Performance

Jake Van Naarden, President

Lilly Oncology Commercial Performance

ONCOLOGY REVENUE GROWTH[1]



KEY PRODUCTS

Verzenio®

CDK4/6 market leader with 2023 worldwide revenue growth of **+56%** and U.S. growth of **+52%**; Approved across metastatic and early breast cancer indications

Retevmo™

Market-leading RET inhibitor with positive uptake since 2020 launch

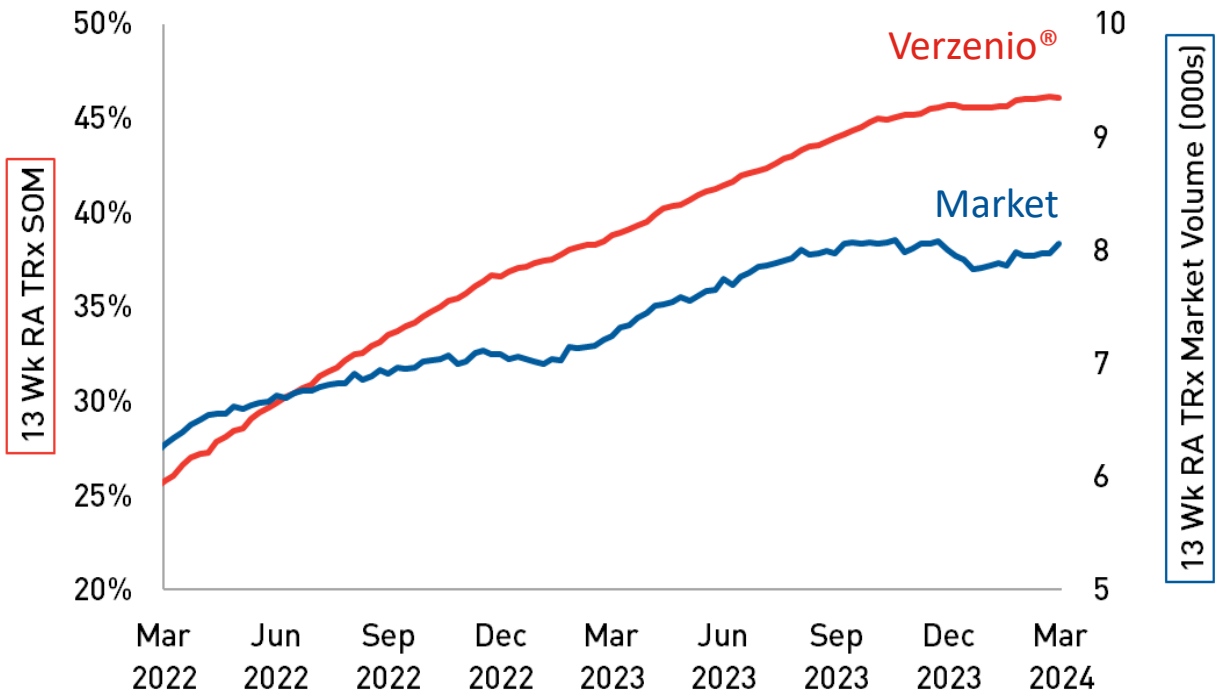
Jaypirca™ pirtobrutinib 50,100 mg tablets

Received accelerated approval for both MCL and CLL patients in 2023; Future potential growth driver as Jaypirca® moves into earlier lines of therapy

1. Excludes Alimta® revenue. CDK = cyclin-dependent kinase; CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; RET = rearranged during transfection.

Verzenio® Performance

U.S. TRx SOM and Market Volume[1]



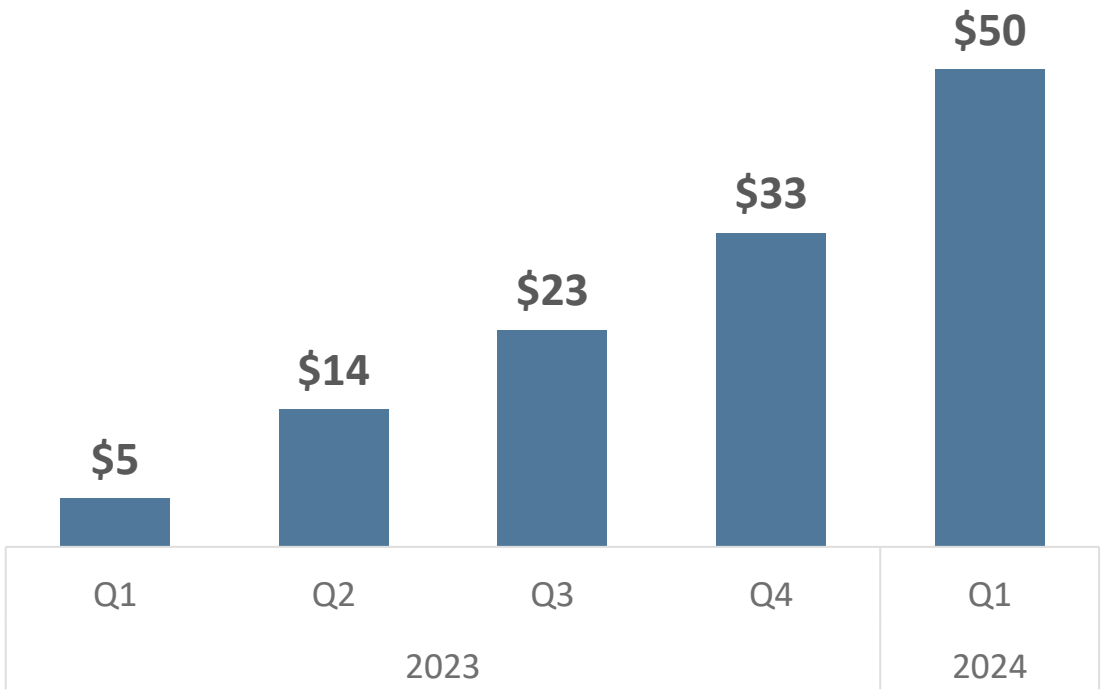
PERFORMANCE DRIVERS

- Strong worldwide sales growth of 40% in Q1 2024 driven by the early breast cancer indication
- Verzenio® has strong market penetration in the U.S., with nearly 60% of high-risk early breast cancer patients receiving Verzenio®
- Q1 2024 U.S. TRx growth of over 32%, which is outpacing growth of the overall CDK4/6 market

1. IQVIA NPA TRx 3MMA, weekly data March 29, 2024. RA = rolling average; SOM = share of market; TRx = total prescriptions.

Jaypirca® Performance

REVENUE PERFORMANCE ($M)

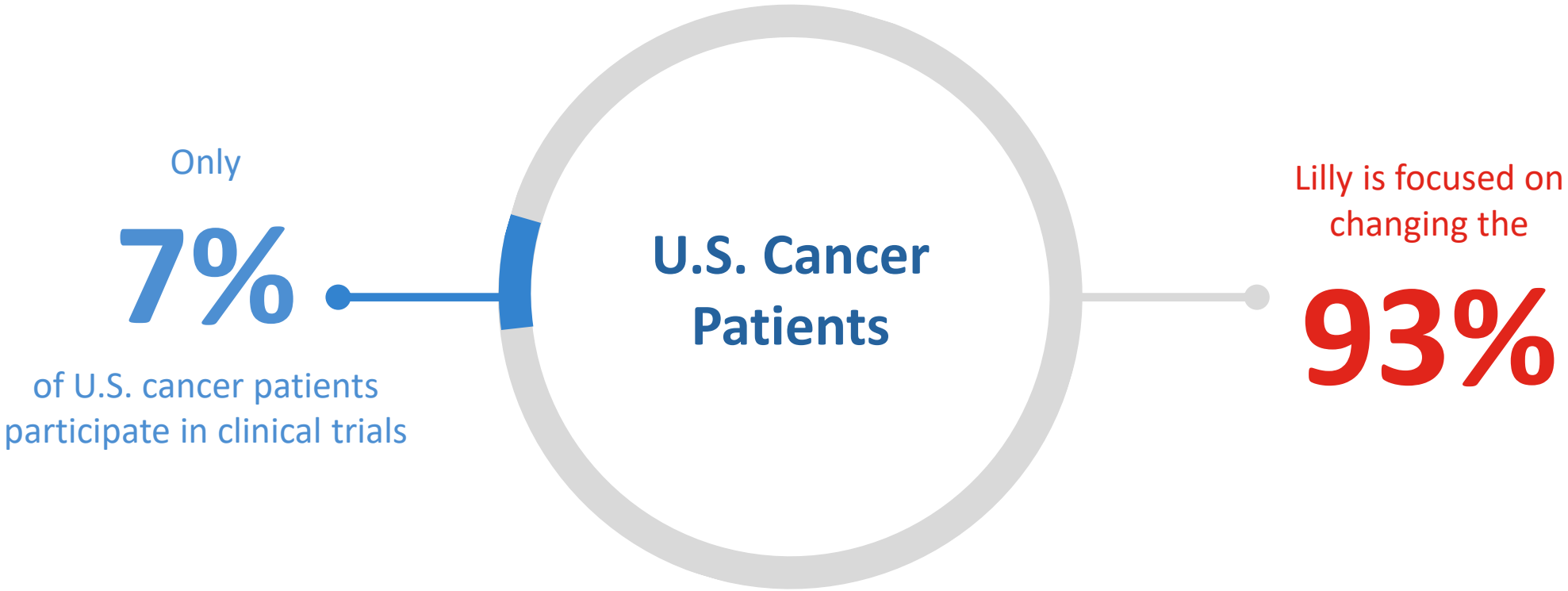


PERFORMANCE DRIVERS

- Jaypirca® received accelerated approval for MCL in January 2023 and CLL in December 2023; CLL indication makes up the majority of new patient starts
- With the growth of BTKi and BCL2 usage, there is a growing number of CLL patients previously treated with both classes of medicines
- NCCN Clinical Practice Guidelines in Oncology gives a 2A recommendation for Jaypirca's® labeled population[1]

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.3.2024. B-Cell Lymphomas v.2.2024 © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed May 29, 2024]. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. BCL2 = B-cell lymphoma; BTKi = Bruton tyrosine kinase inhibitor; MZL = marginal zone lymphoma; NCCN = National Comprehensive Cancer Network®; SLL = small lymphocytic lymphoma.

Working to Speed New Treatments to Patients



Lilly Oncology Portfolio

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Arjun Balar, M.D., Global Clinical Development

Barry Taylor, Ph.D., Chief Scientific Officer

Verzenio®
Imlunestrant
LOXO-783
(PI3Kα H1047R Inhibitor)

Lillian Smyth, M.D.
Global Head, Breast Cancer

Verzenio® Pivotal Studies in HR+, HER2- BC

Verzenio abemaciclib

Abemaciclib is an oral, potent CDK4/6i with greater selectivity for CDK4 than CDK6 which allows continuous dosing due to less myelosuppression

Results presented

2024 ASCO ANNUAL MEETING

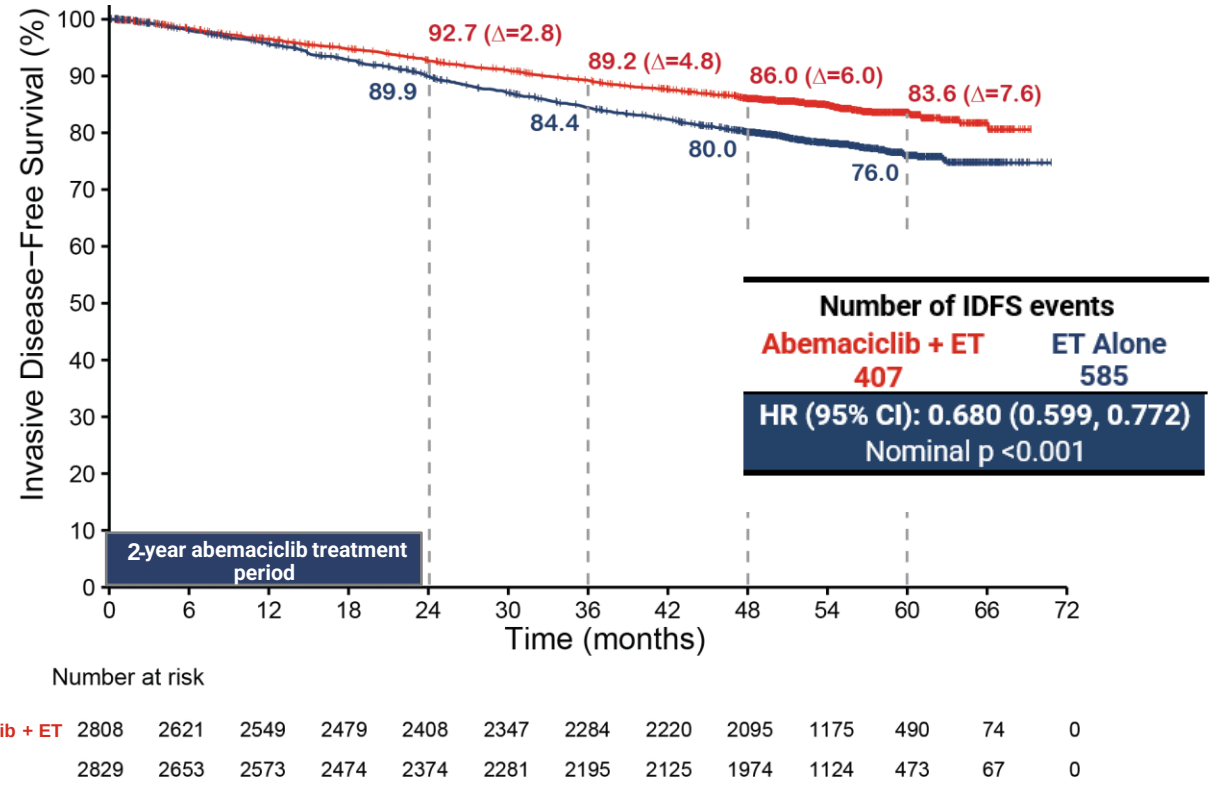
MONARCH-1	MONARCH-2	MONARCH-3	monarchE	postMONARCH (CDK4/6 Sequencing)
Pre-treated ABC	2L ABC	1L ABC	High-risk EBC	2L post-CDK4/6 ABC

Abemaciclib is approved in ABC as monotherapy and in combination with an AI or fulvestrant, and is the first and only CDK4/6 inhibitor approved for high-risk EBC

Common adverse events for Verzenio® include: diarrhea, nausea, infections, anemia, decreased appetite, headache, alopecia, abdominal pain, tiredness, leukopenia, vomiting, and thrombocytopenia

ABC = advanced breast cancer; AI = aromatase inhibitor; BC = breast cancer; CDK = cyclin-dependent kinase; EBC = early breast cancer; HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2; 1L = first line; 2L = second line.

MonarchE: 5-Year Efficacy Results[1]



32% reduction in the risk of developing IDFS event

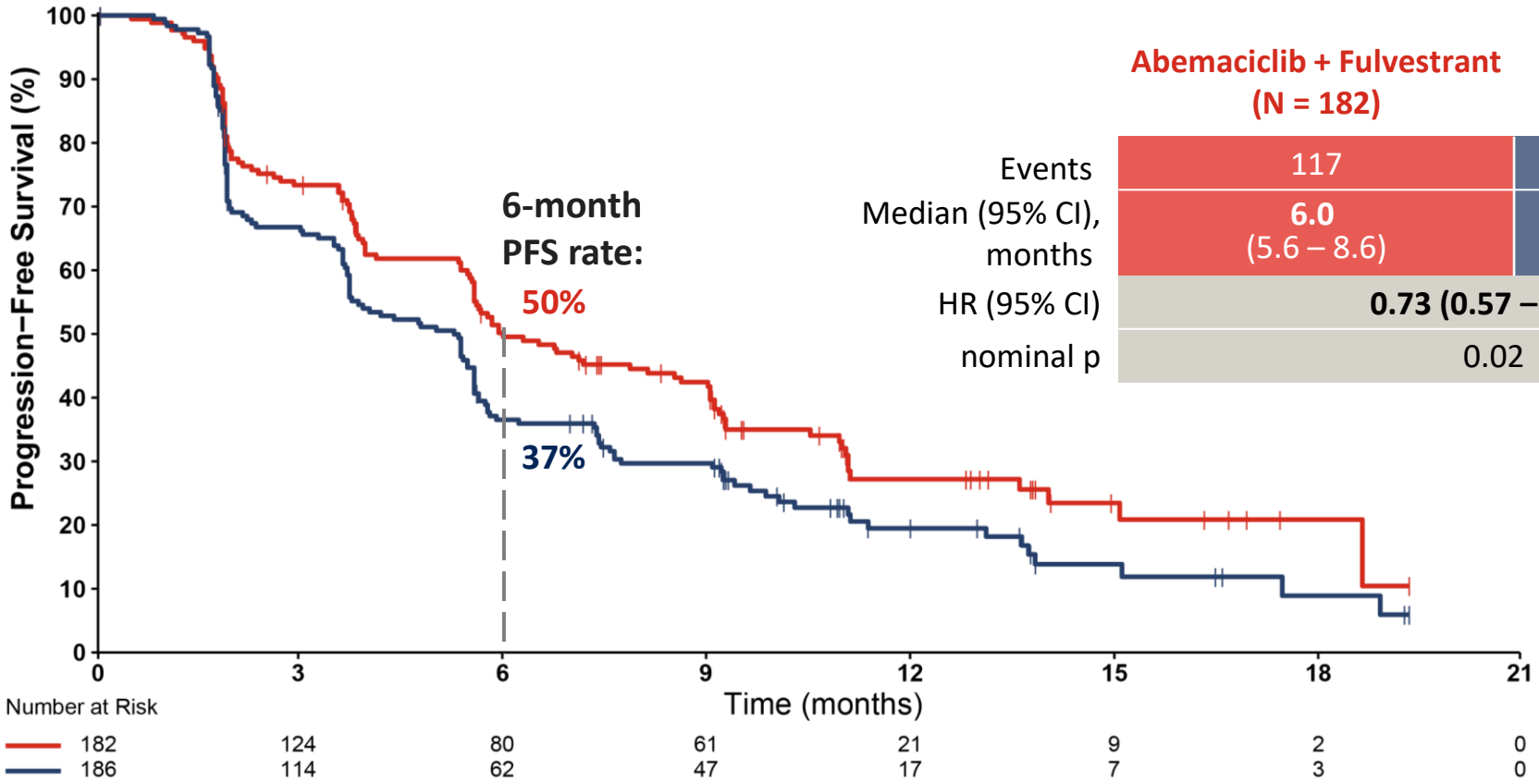
Continued KM curve separation beyond the treatment period

7.6% absolute difference at 5 years

Abemaciclib + ET is the globally approved, standard adjuvant treatment for high-risk EBC (NCCN Category 1 rating[2], strong ASCO guideline recommendation)

1. Nadia Harbeck, MD. ESMO, Madrid, Spain. 20 October 2023. 2.Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.2.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed May 29, 2024. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. ASCO = American Society of Clinical Oncology; ET = endocrine therapy; HR = hazard ratio; IDFS = invasive disease-free survival; KM = Kaplan Meier; NCCN = National Comprehensive Cancer Network.

postMONARCH: Primary Analysis



	Abemaciclib + Fulvestrant (N = 182)	Placebo + Fulvestrant (N = 186)
Events	117	141
Median (95% CI), months	**6.0** (5.6 – 8.6)	**5.3** (3.7 – 5.6)
HR (95% CI)	**0.73 (0.57 – 0.95)**	
nominal p	0.02	

Abemaciclib improved investigator-assessed PFS leading to a 27% reduction in the risk of developing an event

Kallinsky K. Presented at ASCO; May 31 – June 4, 2024. Abstract #LBA1001. PFS = progression-free survival.

postMONARCH: Conclusions

- postMONARCH is the first randomized, placebo-controlled Phase III study to demonstrate benefit of continued CDK4/6 inhibition beyond progression on a CDK4/6i

- Abemaciclib improved PFS in patients with HR+, HER2- ABC with disease progression on prior CDK4/6i + ET, despite the control arm performing better than expected
  - 27% risk reduction for developing a PFS event (HR: 0.73 [0.57 – 0.95])
  - Consistent benefit across multiple prespecified and clinically relevant subgroups, including key biomarker subgroups
  - Consistent improvement across key secondary efficacy endpoints, including PFS by BICR and ORR

- Safety was consistent with the known abemaciclib profile and discontinuation rate was low

Abemaciclib + fulvestrant offers a targeted therapy option after disease progression on a CDK4/6i for patients with HR+, HER2- ABC, not selected for biomarker status

Kallinsky K. Presented at ASCO; May 31 - June 4, 2024. Abstract #LBA1001. BICR = blinded independent central review; ORR = objective response rate.

Imlunestrant

A brain-penetrant oral SERD designed for continuous ER target inhibition (including ESR1-mutant breast cancer)

Current Treatment Landscape

- No clear SOC after progression on 1L therapies in ER+, HER2- ABC
  - Recent evidence (postMonarch) for abemaciclib in this setting
- No SERD approved in combination with CDK4/6i OR in the adjuvant setting

Program Thesis

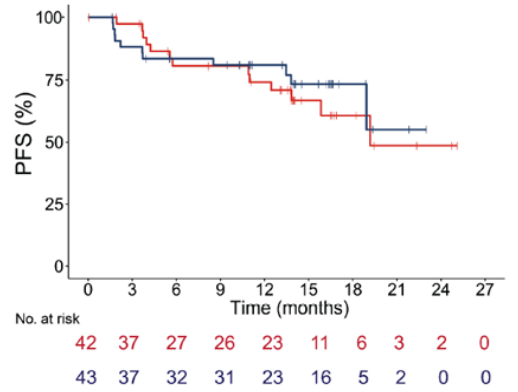
- Develop an oral SERD to differentiate in ABC by combining with abemaciclib
- Displace SOC endocrine therapy in the adjuvant setting

Program Background

- Encouraging early clinical efficacy in 2L post-CDK4/6i setting (alone & with other SOC target therapies)
- Monotherapy was well tolerated and safely combines with SOC
- Pivotal registrational studies ongoing

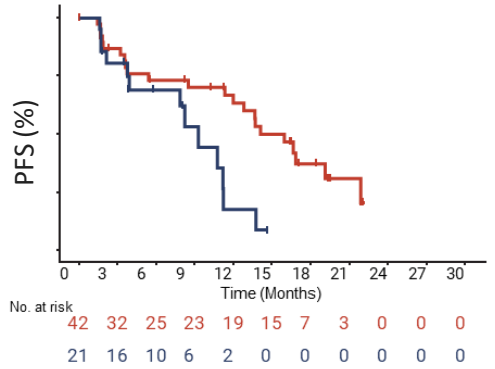
% Progression Free Survival[1]

Group	n	Events	Median (95% CI)
Imlunestrant + abemaciclib	42	13	19.2 (13.8, NA)
Imlunestrant + abemaciclib + AI	43	11	NA (18.9, NA)



% Progression Free Survival[2]

Group	N	Events	Median (95% CI)
Imlunestrant + everolimus	42	22	19.2 (13.8, NA)
Imlunestrant + alpelisib	21	13	9.2 (3.7, 11.1)



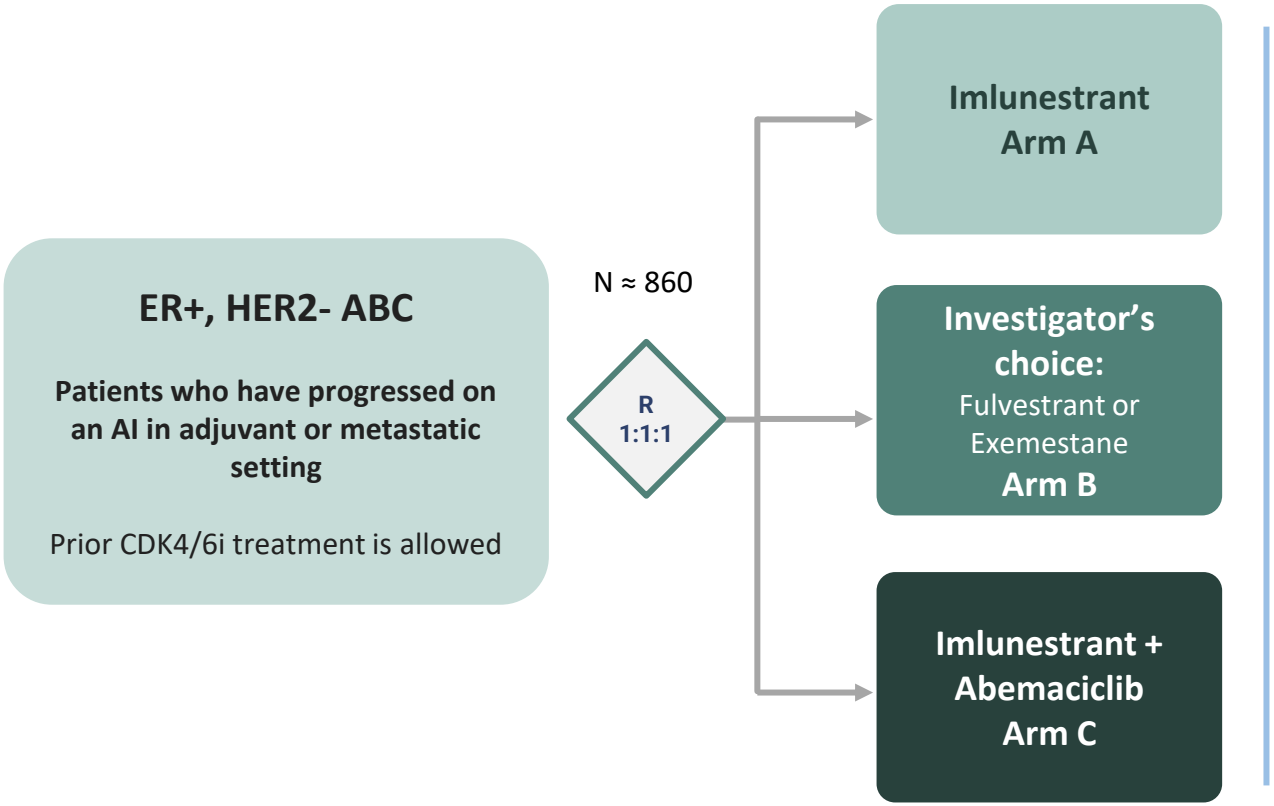
Most common any grade TRAEs: diarrhea, nausea, fatigue, and neutropenia

SERD = selective estrogen receptor degrader; SOC, standard of care.

1. Jhaveri KL, et al. Presented at SABCS 2023. Abstract PS15-09. 2. Jhaveri KL, et al. Presented at ESMO 2023. Abstract 383 MO.

Imlunestrant

ONGOING PHASE III REGISTRATIONAL TRIAL: EMBER-3



- Dual primary endpoints: PFS in ITT and ESR1-mutant populations
- First evaluation of an oral SERD + CDK4/6 inhibitor in a randomized phase III trial in the 2L setting
- Potential for approval with dual indication (monotherapy and combination with Verzenio®)
- Data expected in 2H 2024

ClinicalTrials.gov. NCT05514054. ITT = intent-to-treat; PFS = progression-free survival; R = randomization.

Imlunestrant

ONGOING PHASE III REGISTRATIONAL TRIAL: EMBER-4

ER+, HER2- EBC

Patients who have received 2-5 years of adjuvant ET with an increased risk of recurrence

Prior CDK4/6i treatment is allowed

N ≈ 6,000

R 1:1

Imlunestrant (5 years)

Investigator's choice ET Tamoxifen or AI (5 years)

- Sequencing strategy for patients at increased risk of recurrence - addresses the full continuum of adjuvant treatment
  - Patients can sequence from upfront therapy with abemaciclib + ET to an oral SERD to complete adjuvant therapy
- Largest oncology trial at Lilly
- Estimated primary completion in 2027

Enrolling

ClinicalTrials.gov. NCT05514054. EBC = early breast cancer; ET = endocrine therapy.

LOXO-783

A highly mutant-selective PI3Kα H1047R allosteric inhibitor

Current Treatment Landscape

- PI3Ka H1047R mutations occur in ~15% of breast cancer
- Approved PI3Kα and AKT inhibitors are not mutant-selective, leading to wildtype-mediated toxicity, including hyperglycemia, skin, and GI toxicity

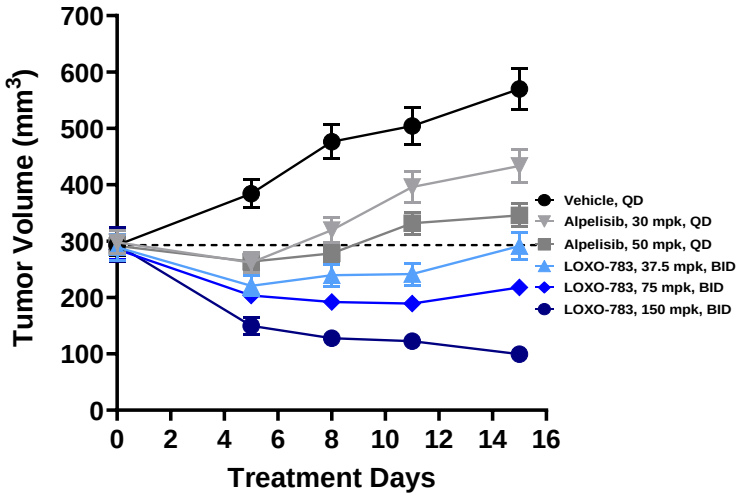
Program Thesis

- Develop a mutant-selective PI3Kα H1047R inhibitor with selectivity over wildtype PI3Kα leading to superior efficacy and tolerability

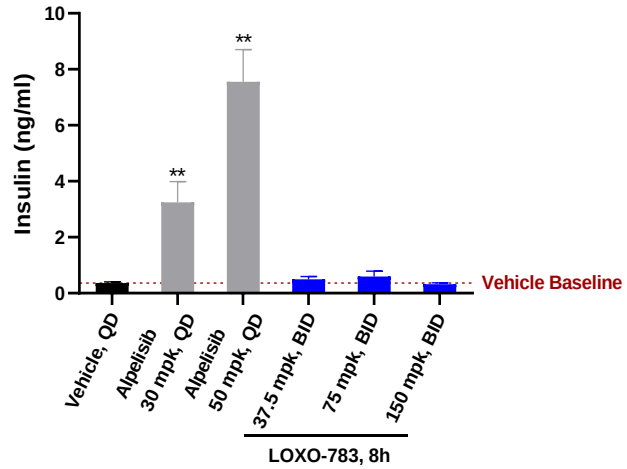
Program Background

- Achieves significant tumor regression without increase in insulin or C-peptide and shows additive efficacy when combined with SOC treatments in vivo[1,2]
- Phase I trial (PIKASSO) FHD in ‘22, ongoing trial
- Part of a broad discovery campaign against this target profile

T47D
(PI3Kα H1047R)



Plasma insulin (ng/mL), NSG mice
(24 days repeat dosing)



1. Klippel A, et al. Presented at AACR-NCI-EORTC Virtual Meeting; October 11-15, 2021; 2. Puca L, et al. Presented at SABCS; December 6-10, 2022. NSG = NOD scid gamma; SOC = standard of care.

Jaypirca®
FRα ADC

John Pagel, M.D., Ph.D.
Global Head, Hematology

Jaypirca® Pivotal Studies

Jaypirca® is the only FDA-approved non-covalent BTK inhibitor

Jaypirca™ pirtobrutinib 50,100 mg tablets

● Results presented ○ Study ongoing

BRUIN	BRUIN MCL-321	BRUIN CLL-321	BRUIN CLL-313	BRUIN CLL-322	BRUIN CLL-314
R/R CLL/SLL and MCL	BTKi-naïve MCL	Post-BTKi CLL	Tx-naïve CLL	CLL	BTKi-naïve CLL
	H2H vs BTK	Monotherapy	Monotherapy	H2H PirtoVenR vs VenR	H2H vs Ibrutinib

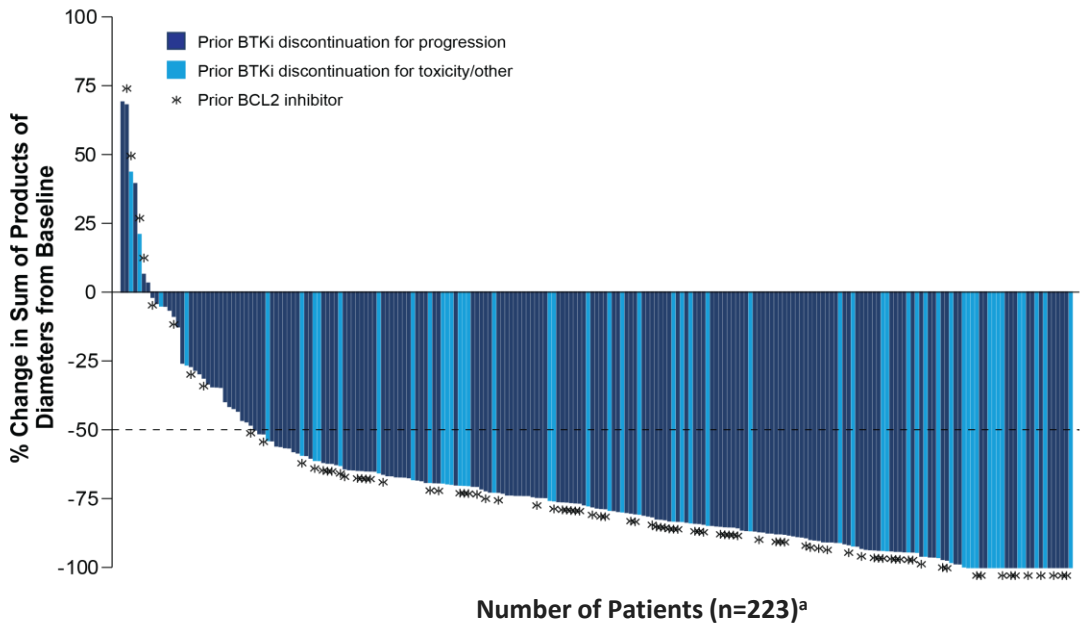
Jaypirca® is approved[1] for the treatment of relapsed or refractory:

- MCL after two lines of therapy, including a prior BTKi
- CLL after two lines of therapy, including a prior BTKi and BCL2i

1. Jaypirca® received accelerated approval approved based on how many people responded to treatment. Studies are ongoing to confirm the benefit of Jaypirca® for this use. BCL2i = B-cell lymphoma inhibitor; BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; H2H = head to head; MCL = mantle cell lymphoma; PirtoVenR = pirtobrutinib + venetoclax + rituximab; SLL = small lymphocytic lymphoma; Tx = treatment; VenR = venetoclax + rituximab.

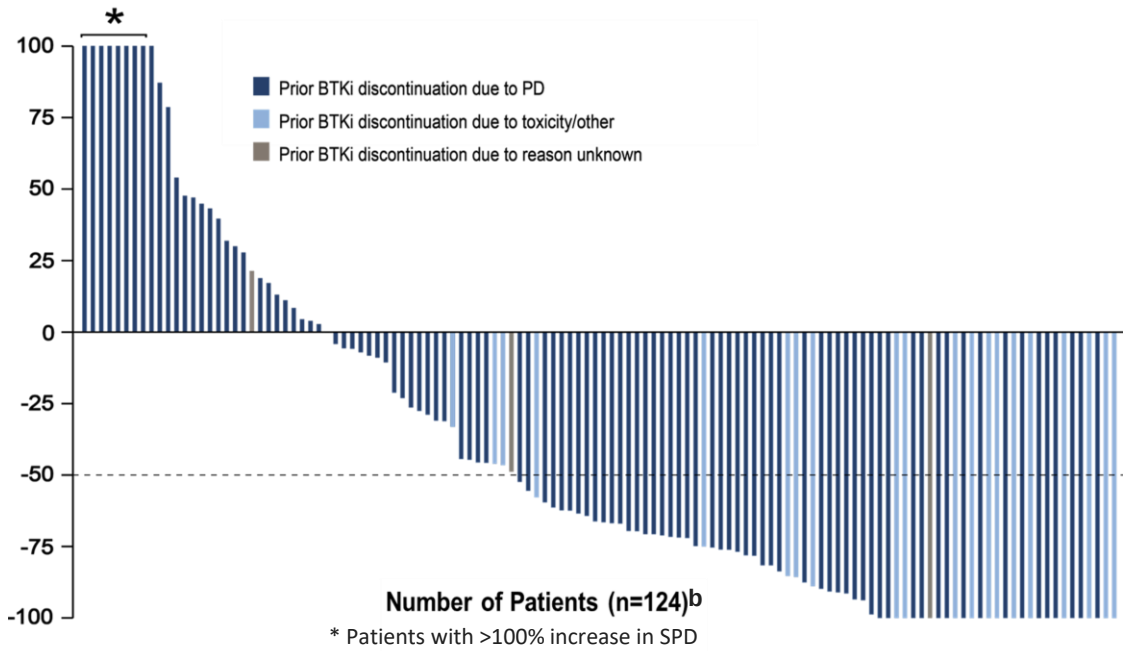
Jaypirca®

CLL/SLL: Pirtobrutinib efficacy with prior cBTKi



a. Data for 24/247 patients who received prior cBTKi are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up.

MCL: Pirtobrutinib efficacy with prior cBTKi



b. Data for 28/152 patients who received prior cBTKi are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up.

Jaypirca® is the first and only approved non-covalent BTK inhibitor in both CLL & MCL

Common adverse events for Jaypirca® include: tiredness, muscle pain, joint pain, bone pain, diarrhea, COVID-19, bruising, and cough

Mato, et al. Presented at ASH; December 10-13, 2022; Cohen, et al. Presented at ASH; December 6-15, 2023. cBTK = covalent Bruton tyrosine kinase; BCL2 = B-cell lymphoma; CT = computed tomography; PD = product of diameters; SD = stable disease; SPD = sum of the product of diameters.

Pivotal Studies

Jaypirca™ pirtobrutinib 50,100 mg tablets

	BRUIN MCL-321	BRUIN CLL-321	BRUIN CLL-313	BRUIN CLL-322 (Enrolling)	BRUIN CLL-314	BRUIN CLL-18 (Est. start Q4 2024)
DISEASE SETTING	R/R MCL	R/R CLL	1L CLL	R/R CLL	1L and R/R CLL	1L CLL
REGIMEN	Continuous dosing	Continuous dosing	Continuous dosing	Fixed duration with VenR	Continuous dosing	Fixed duration with Ven 2 active arms, one MRD-guided
COMPARATOR	Covalent BTK	IdelaR / BendaR	BendaR	VenR	Ibrutinib	VenO

Comprehensive Phase III clinical development plan

BendaR = bendamustine plus rituximab; IdelaR = idelalisib plus rituximab; MRD = minimal residual disease; R/R = relapsed/refractory; VenO = venetoclax plus obinutuzumab; VenR = venetoclax plus rituximab; 1L = first line.

FRα ADC

A next-generation ADC targeting folate receptor α at all expression levels with improved therapeutic index

Current Treatment Landscape

- Elahere™ is limited to high FRα tumor expression levels and is associated with ocular toxicity

Program Thesis

- Establish a new standard of care FRα ADC that is effective, regardless of FRα expression levels, with low toxicity

Program Background

- Composed of an Fcγ silent monoclonal antibody linked to a topoisomerase-1 payload, exatecan, via a novel PSAR linker with a DAR of 8
- Achieves preclinical tumor regression in low and moderate FRα-expressing models w/o evidence of ocular toxicity, ILD, or neuropathy
- Phase I trial has begun dosing patients

DAR = drug-to-antibody ratio; ILD = interstitial lung disease; PSAR = polysarcosine.

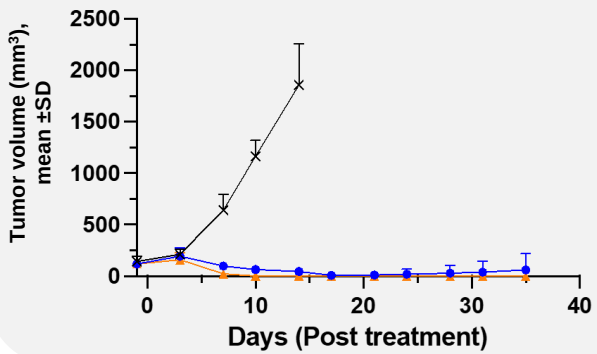
FRα ADC

FRα expression level

++++ +++ ++ +

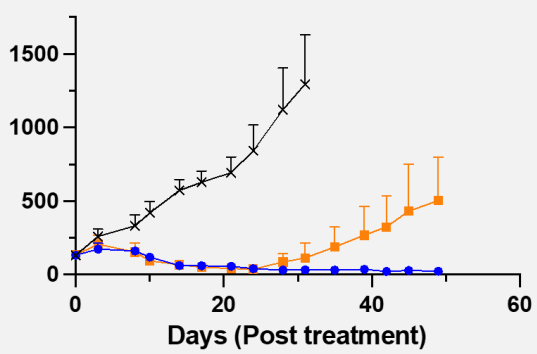
Cervical Cancer

FRα ++++ model (KB)



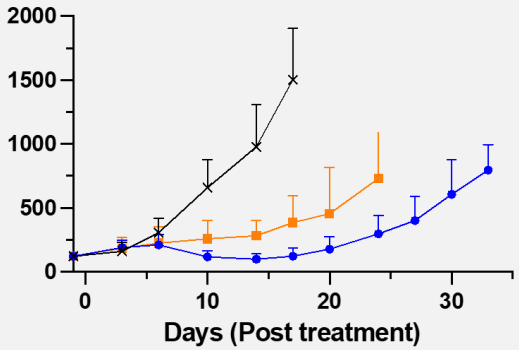
Ovarian Cancer

FRα +++ model (IGROV1)



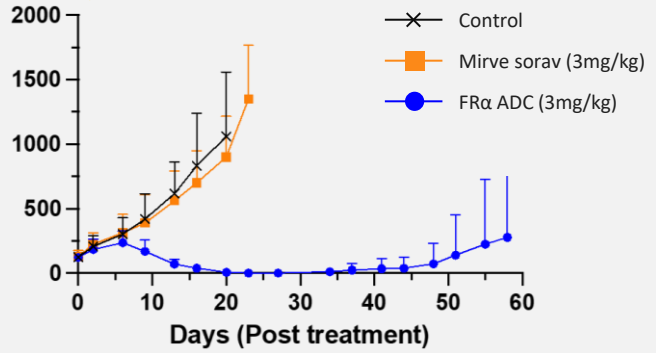
Ovarian Cancer

FRα ++ model (OV90)



Colorectal Cancer

FRα + model (SW-620)



In vivo activity in low FolR1-expressing ovarian tumors and other tumor types that are not sensitive to Elahere™[1]

1. Viricel W, et al. Presented at AACR; April 14-19, 2023. Mirve sorav = mirvetuximab soravtansine.

Retevmo®
Olomorasib
KRAS G12D Inhibitor
PAN-KRAS Inhibitor

Geoff Oxnard, M.D.
Global Head, Thoracic Cancer

Retevmo® Pivotal Studies

Used to treat certain cancers caused by abnormal RET genes

Retevmo® selpercatinib

● Results presented ○ Study ongoing

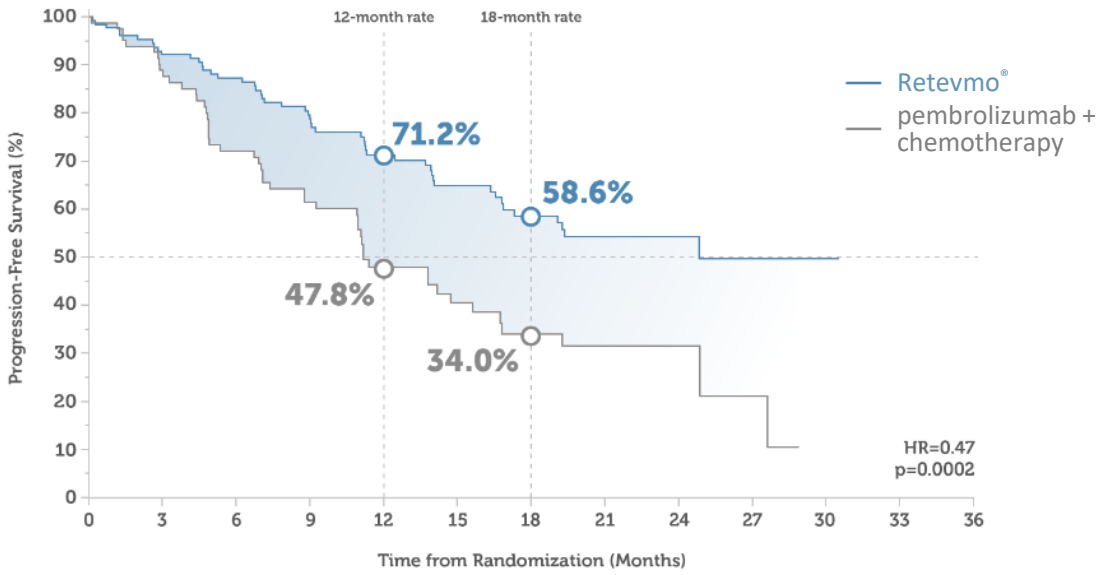
LIBRETTO-001	LIBRETTO-431	LIBRETTO-531	LIBRETTO-432
RET+ metastatic cancers in NSCLC, thyroid, and tumor agnostic	RET fusion+ advanced or metastatic NSCLC	RET mut+ advanced or metastatic MTC	RET fusion+ adjuvant NSCLC

First FDA-approved treatment for people with RET-positive advanced NSCLC, thyroid cancers, and certain other cancers

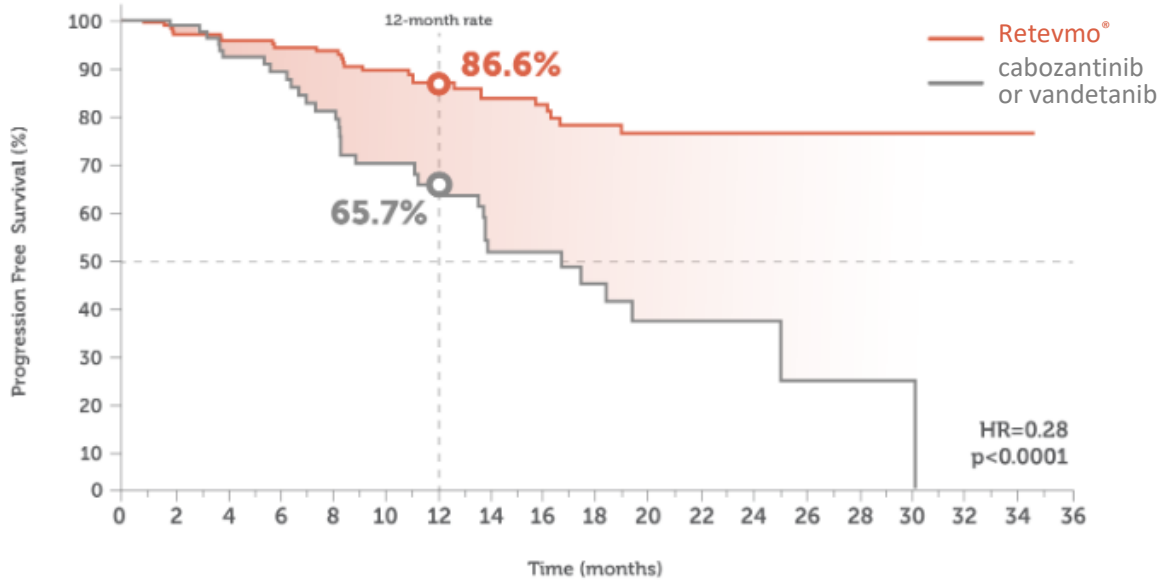
FDA = Food and Drug Administration; MTC = medullary thyroid carcinoma; NSCLC = non-small cell lung cancer.

Retevmo®

Retevmo® vs KEYNOTE-189 in 1L NSCLC[1]



Retevmo® vs MKI in MTC[2]



Common adverse events for Retevmo® include: edema, diarrhea, tiredness, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache

1. Loong, et al. Presented at ESMO; October 20-24, 2023; 2. Hadoux, et al. Presented at ESMO; October 20-24, 2023.
HR = hazard ratio; MKI = multi-targeted kinase inhibitor.

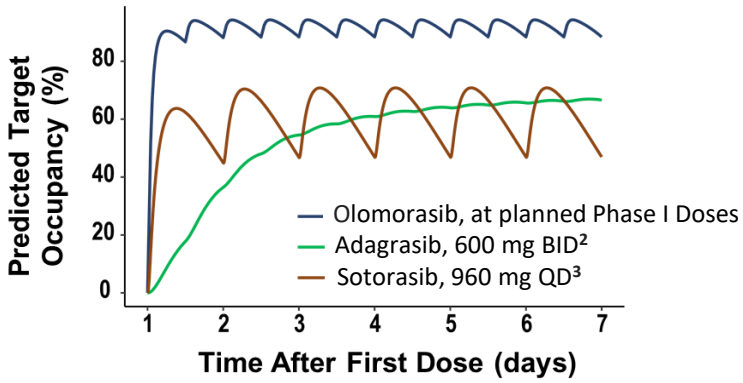
Lilly KRAS Portfolio

Olomorasib (KRAS G12C)	KRAS G12D	Pan-KRAS
2024 Phase III Start	**2024 IND Submission**	**2024 IND Submission**
2nd generation G12C inhibitor	Highly potent non-covalent inhibitor of KRAS G12D	Highly potent non-covalent isoform-selective pan-KRAS inhibitor
Combinable with IO	Achieved oral bioavailability in preclinical species	Achieved oral bioavailability in preclinical species

KRAS G12D & pan-KRAS developed from pharmacologic insights generated by olomorasib

Olomorasib

A potent and selective 2nd -generation KRAS G12C inhibitor to combine with PD-1 inhibitor



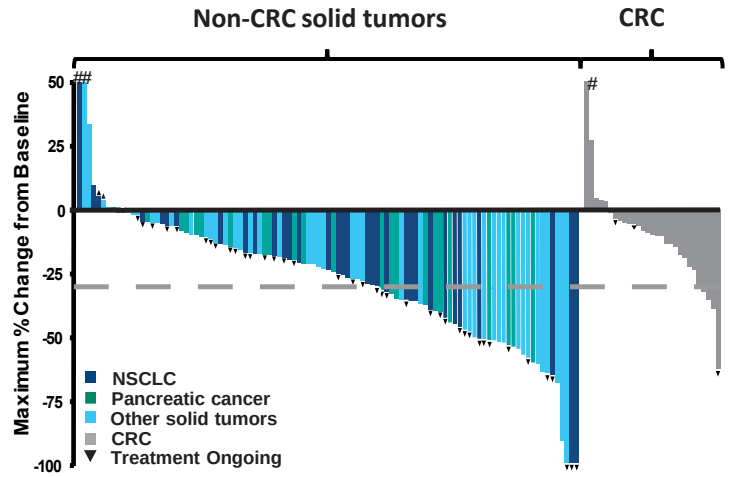
Highly potent covalent inhibitor, with potential for >90% clinical target occupancy[4]

Current Treatment Landscape

- KRAS G12C mutations occur in up to 15% of NSCLC[1]
- Currently approved 1st-generation KRAS G12C inhibitors have limitations due to tolerability, including ability to combine with PD-1 inhibitor

Program Thesis

- A potent and selective KRAS G12C inhibitor will be safely combinable with IO to improve outcomes in 1L NSCLC

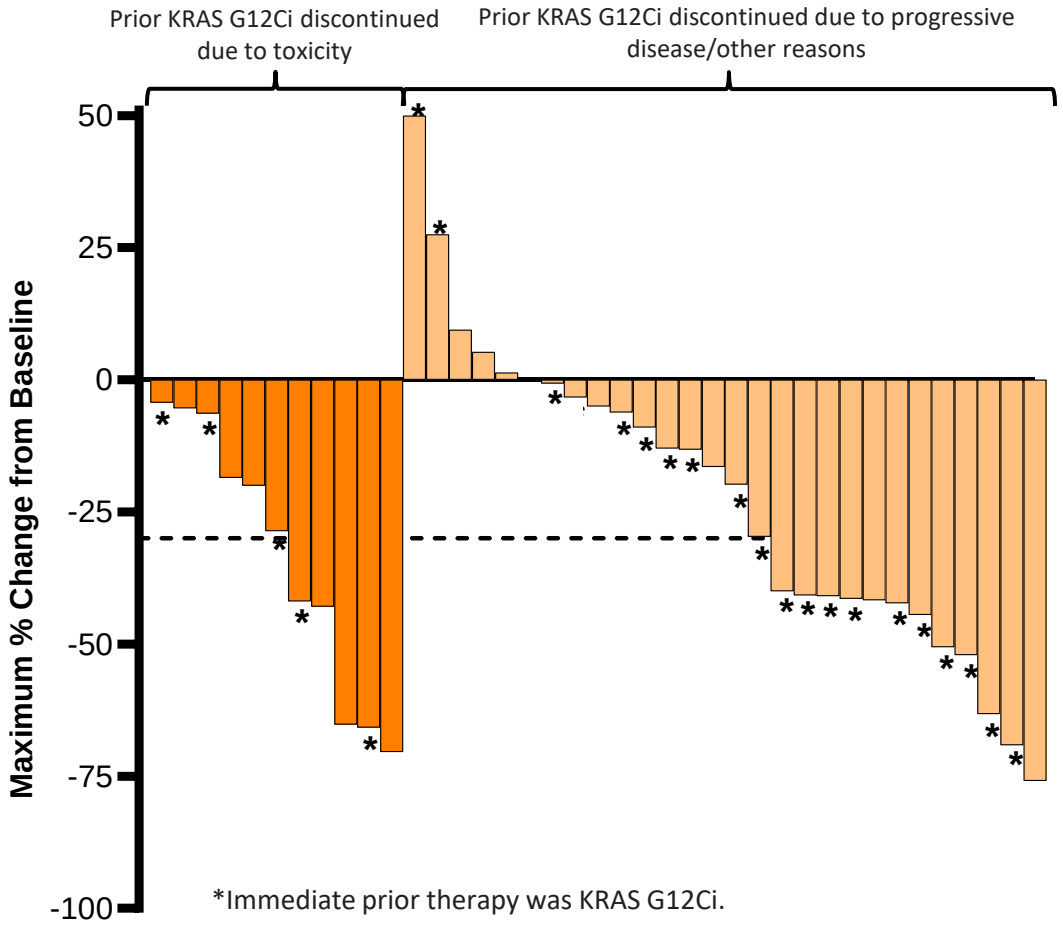


Efficacy in KRAS G12Ci-naïve Solid Tumors[5]

1. Lee A. Target Oncol. 2022;17:727-33. 2. Janne PA, et al. 2020; 3. Hong DS, et al. N Engl J Med. 2020;383:1207-17; 4. Sheng-Bin P, et al. 2021; 5. Heist RS, et al. Presented at ASCO; May 31 – June 4, 2024. Abstract #3007.

Data cutoff date of 18 Mar 2024.

Olomorasib Monotherapy



*Immediate prior therapy was KRAS G12Ci.

Efficacy Evaluable Patients	Prior KRAS G12Ci discontinued due to	
	Toxicity (n = 11)	Progressive disease/ other reasons (n = 28)
Objective response rate, %	46	39
Disease control rate, %	100	75

- KRAS G12Ci-pretreated NSCLC, median PFS was 8.1 months
- Favorable safety profile, including in patients with prior intolerance to other G12C inhibitors
  - Grade 1 diarrhea was most common TRAE
  - 1 patient discontinued due to a TRAE

Monotherapy efficacy and safety in KRAS G12Ci-pretreated NSCLC

Heist RS, et al. Presented at ASCO; May 31 – June 4, 2024. Abstract #3007. PFS = progression-free survival; TRAE = treatment-related adverse events.

Olomorasib Monotherapy

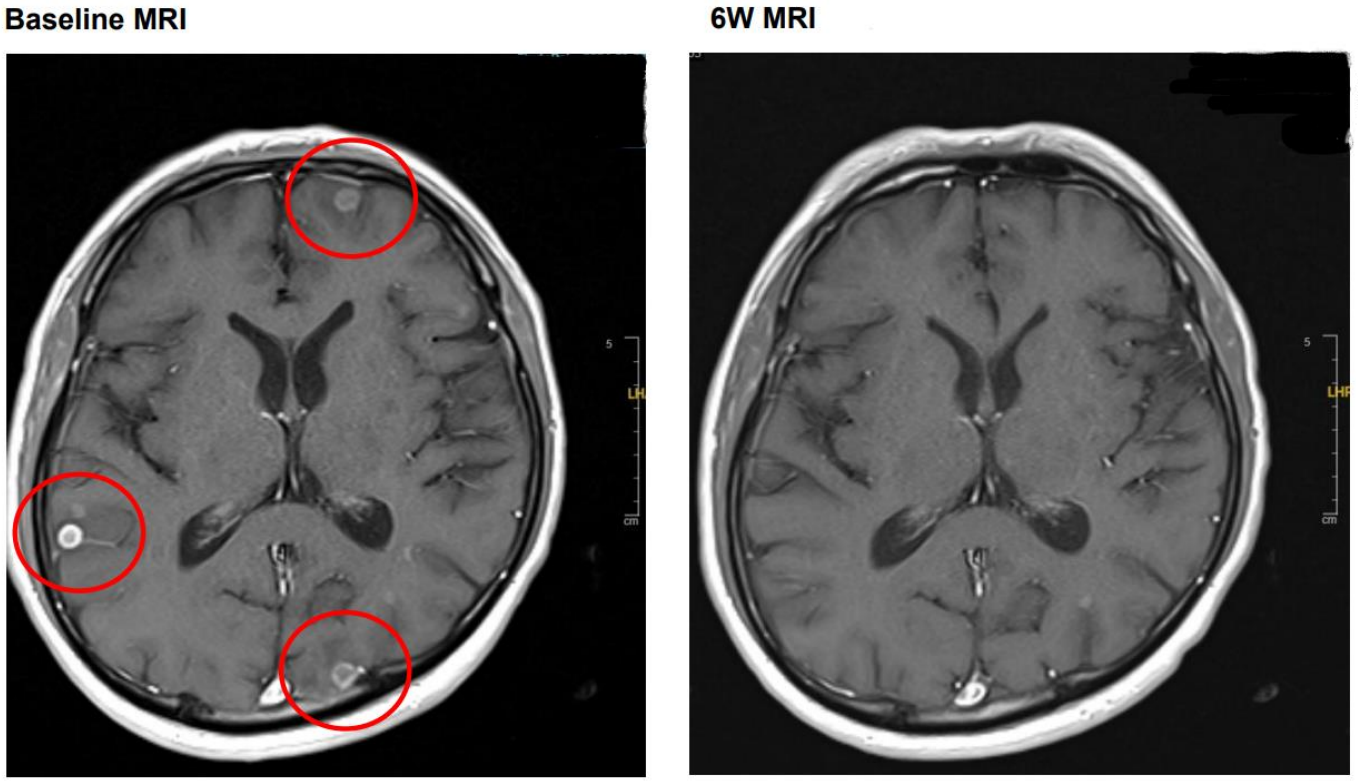


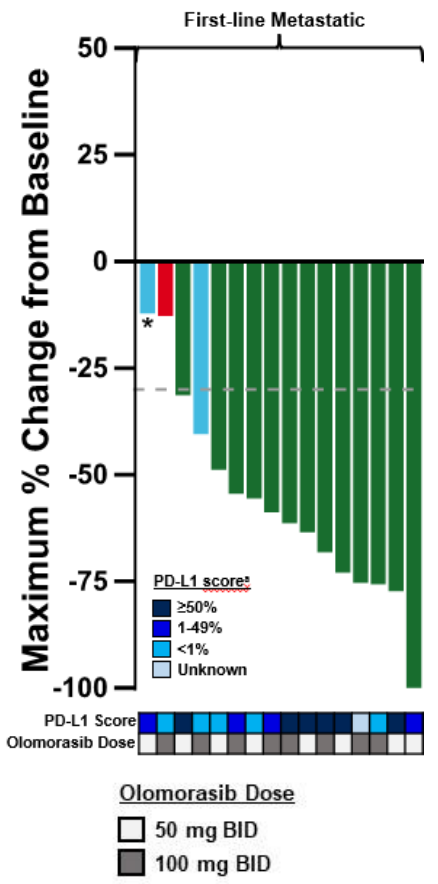
Image courtesy of Toshio Shimizu, M.D., Ph.D., Wakayama Medical University Hospital

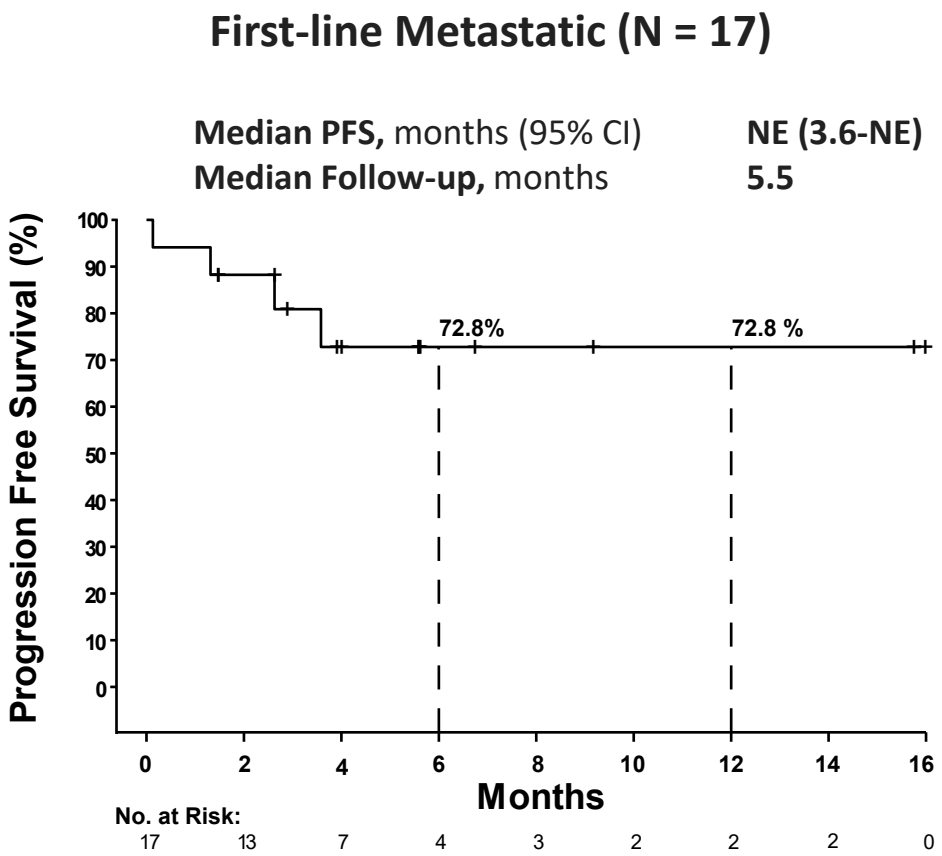
- CNS activity is a key feature for targeted therapies in advanced NSCLC
- CNS activity seen in NSCLC patients with measurable brain metastases treated with olomorasib

CNS activity supports the potential for durable effect in NSCLC

Heist RS, et al. Presented at ASCO; May 31 – June 4, 2024. Abstract #3007. CNS = central nervous system; MRI = magnetic resonance imaging; 6W = 6 weeks.

Olomorasib + Pembrolizumab





Efficacy Evaluable Patients	First-line Metastatic (N=17)
Overall response rate, % (n/N)	**77% (13/17)**
Best overall response	
CR, n (%)	-
PR, n (%)	13 (76)
SD, n (%)	2 (12)
PD, n (%)	1 (6)
NE, n (%)	1 (6)
DCR, n (%)	**88% (15/17)**

Responses observed across all PD-L1 expression levels

Burns T, et al. Presented at ASCO; May 31 – June 4, 2024. Abstract #8510. CR = complete response; NE = not evaluable; PD = progressive disease; PD-L1 = programmed death ligand 1; PR = partial response; SD = stable disease.

Olomorasib + Pembrolizumab

All Doses and Patients (50 + 100 mg BID, N = 64)

Adverse Event	Treatment-Related AEs[a], %, ≥10%				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Patients with ≥1 TRAE	70	20	23	25	2
Diarrhea	23	8	3	13	-
Fatigue	16	8	8	-	-
ALT increased	20	11	3	6	-
Pruritus	19	11	5	3	-
Nausea	14	6	8	-	-
AST increased	16	6	2	8	-

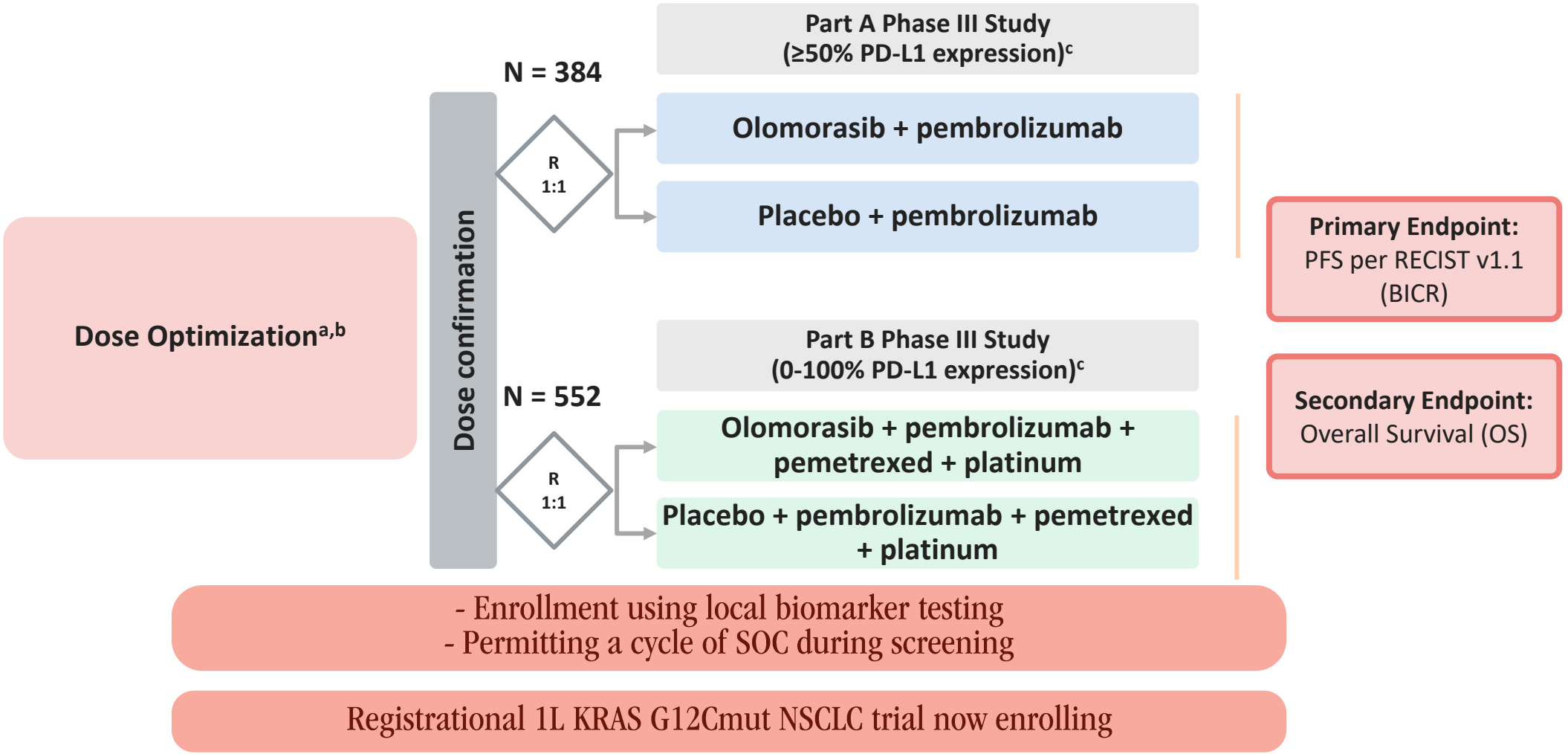
1 patient had a grade 4 TRAE (pneumonitis). [a]TRAEs are olomorasib and/or pembrolizumab related.

TRAEs led to permanent discontinuation of olomorasib only in 3% of patients (2/64) and pembrolizumab only in 11% of patients (7/64); 5% of patients (3/64) discontinued both drugs due to TRAEs

Olomorasib + pembrolizumab AE profile well suited for 1L NSCLC development

Burns T, et al. Presented at ASCO; May 31 – June 4, 2024. Abstract #8510. ALT = alanine aminotransferase; AST = aspartate aminotransferase.

SUNRAY-01: 1L Metastatic KRAS G12C NSCLC



a. Participants should be suitable for pembrolizumab monotherapy. b. PD-L1 expression 0-100%, N~40 for each study part (randomized Dose Optimization and Safety Lead-In Part B). c. Participants with PD-L1 ≥50% are eligible to be enrolled to Part A or Part B at the discretion of the investigator. Heist RS, et al. Presented at ASCO; May 31 – June 4, 2024. Abstract #3007. BICR = blinded independent central review; PD-L1 = programmed death ligand 1; R = randomization; SOC = standard of care.

KRAS G12D Inhibitor

An orally bioavailable, highly potent, and selective KRAS G12D inhibitor

Current Treatment Landscape

- KRAS G12D mutations occur in upwards of 40% and 15% of PDAC and CRC, respectively, and occur less frequently in other solid tumors[1]
- High unmet need - No approved KRAS G12D inhibitors

Program Thesis

- Develop an oral, highly selective KRAS G12D inhibitor that is selective over wild-type KRAS and other targets

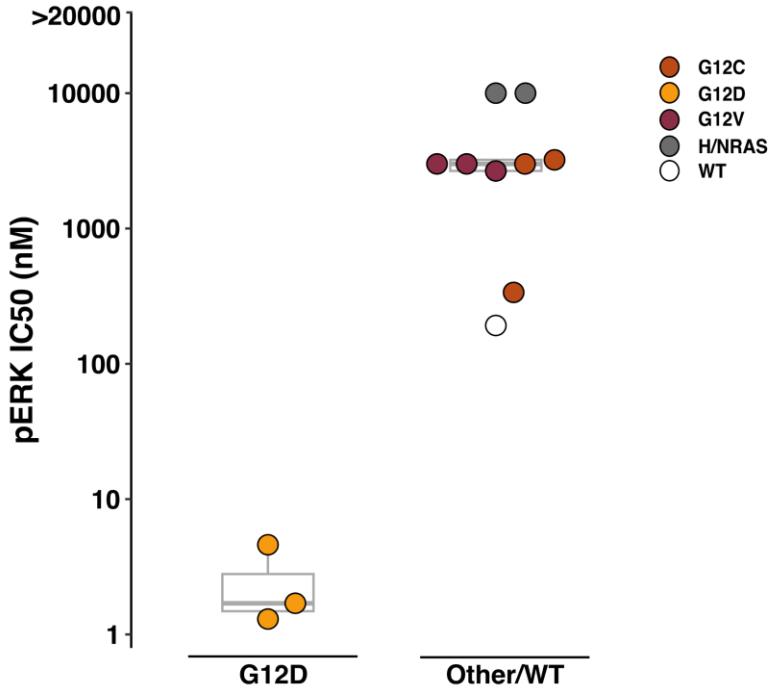
Program Background

- Achieved oral bioavailability in preclinical species providing tonic target coverage
- Potently inhibits KRAS G12D and is selective over wild-type KRAS, HRAS, and NRAS
- IND submission planned 2024

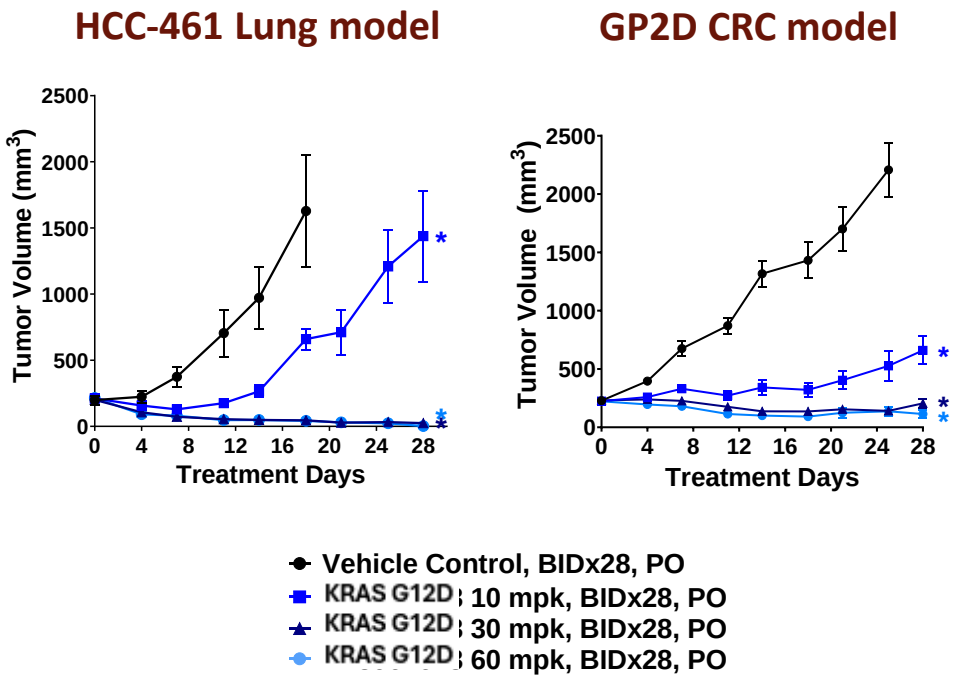
1. Lin TA, et al. J Clin Oncol. 2023;41:3074-5. CRC = colorectal cancer; PDAC = pancreatic ductal adenocarcinoma.

KRAS G12D Inhibitor

Pathway Inhibition



Cancer Cell Models



Highly potent and selective in preclinical models

1. Iyer C, et al. Presented at AACR-NCI-EORTC; October 11-15, 2023.
pERK = protein kinase R-like endoplasmic reticulum kinase.

Pan-KRAS Inhibitor

An orally bioavailable, highly potent pan-KRAS inhibitor

Current Treatment Landscape

- KRAS mutations occur in approximately 1 of every 7 cancers[1]
- Multi-KRAS inhibitors have demonstrated challenging toxicity

Program Thesis

- Develop an oral multi-mutant KRAS inhibitor that spares HRAS, NRAS, and other off-targets

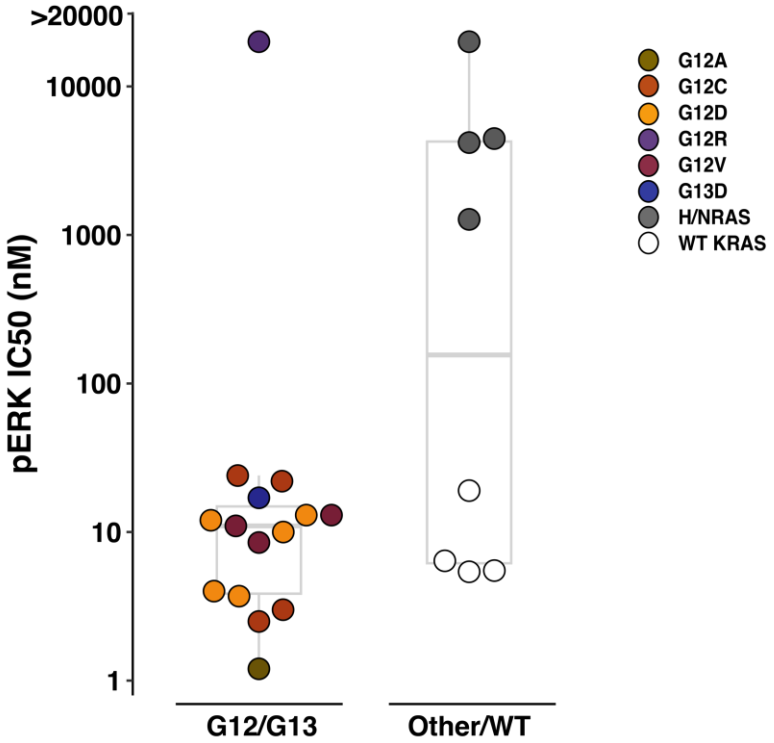
Program Background

- Achieved oral bioavailability in preclinical species providing tonic target coverage
- Potently inhibits KRAS G12D, G12C, G12V and various additional known oncogenic KRAS mutations and wild-type KRAS, and is selective over HRAS, NRAS, and other off-targets
- IND submission planned 2024

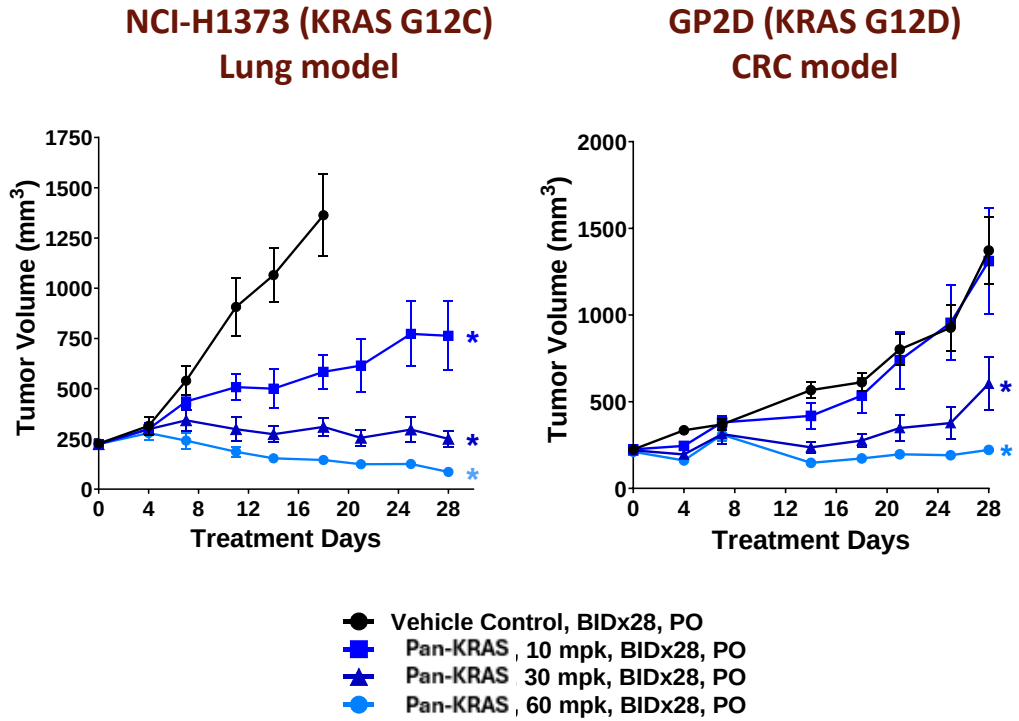
1. Hofmann MH, et al. Cancer Discovery. 2022;12:924-37.

Pan-KRAS Inhibitor

Pathway Inhibition



Cancer Cell Models



Highly potent and isoform selective in preclinical models

1. Prieto, et al. Presented at AACR-NCI-EORTC; October 11-15, 2023. pERK = protein kinase R-like endoplasmic reticulum kinase.

LOXO-435 (FGFR3 Inhibitor) Nectin-4 Targeted ADCs

Arjun Balar, M.D.
Global Clinical Development

LOXO-435 (FGFR3 Inhibitor)

A highly potent isoform-selective FGFR3 inhibitor

Current Treatment Landscape

- Activating FGFR3 alterations are found in 15-20% of metastatic urothelial cancer
- Approved pan-FGFR inhibitors exhibit limited efficacy, dose-limiting off-target toxicities, and susceptibility to resistance mutations

Program Thesis

- Develop a highly potent and isoform-selective FGFR3 inhibitor with preserved potency against gatekeeper resistance mutations

Program Background

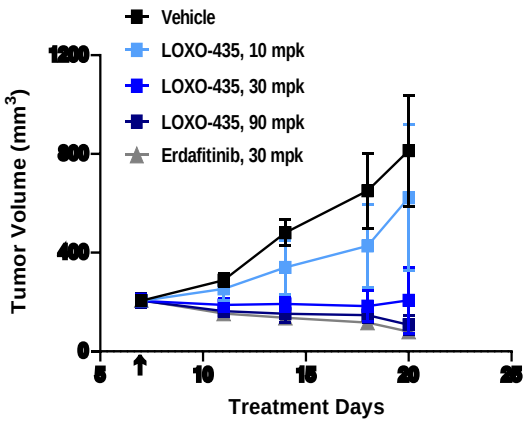
- Isoform-selective FGFR3 inhibitor that has shown antitumor activity in vivo, with preserved potency against FGFR3 gatekeeper resistance mutants[1]
- Spares FGFR1 and FGFR2 in preclinical in vivo models, potentially avoiding dose-limiting hyperphosphatemia and other clinical adverse events[2]
- Phase I FHD achieved in 2023, trial is ongoing

1. Ballard JA, et al. Mol Cancer Ther. 2021; 2. Repetto M, et al. Expert Rev Clin Pharmacol. 2021;14:1233-52. FGFR = fibroblast growth factor receptor, FHD = first human dose.

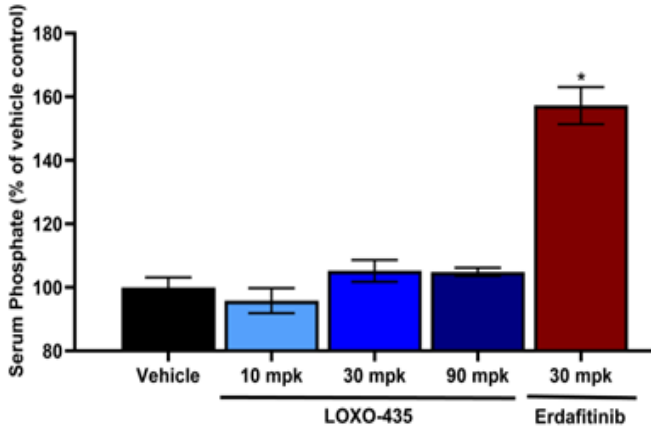
LOXO-435 (FGFR3 Inhibitor)

	Enzyme Inhibition IC_{50} (nM)				Fold Selectivity	
	FGFR1	FGFR2	FGFR3	FGFR3 V555M	FGFR3 over FGFR1	FGFR3 over FGFR2
Erdafitinib	0.3	0.6	0.2	1218.0	1.5x	2.0x
Pemigatinib	0.5	0.3	1.0	752.0	0.5x	0.3x
Infigratinib	0.4	0.7	0.3	579.8	1.3x	0.6x
Futibatinib	0.7	0.4	0.4	14.4	1.8x	1.8x
LOXO-435	108.2	19.7	0.3	1.1	361x	66x

UMUC-14 (FGFR3 S249C)



Serum phosphate in athymic mice (3.5d BID treatment)



Highly isoform-selective for FGFR3, with gatekeeper activity, and observed tumor regressions without hyperphosphatemia in preclinical experiments

Nectin-4 Targeted ADCs

Two opportunities to improve outcomes for patients

Current Treatment Landscape

- Treatment resistance to Padcev® is a key unmet need in metastatic urothelial cancer
- Nectin-4 remains overexpressed post-Padcev®[1]
- Efficacy of Padcev® is not well established in non-urothelial solid tumors

Program Thesis

- Overcome Padcev® treatment resistance and toxicities; achieve efficacy in other Nectin-4 expressing tumor types

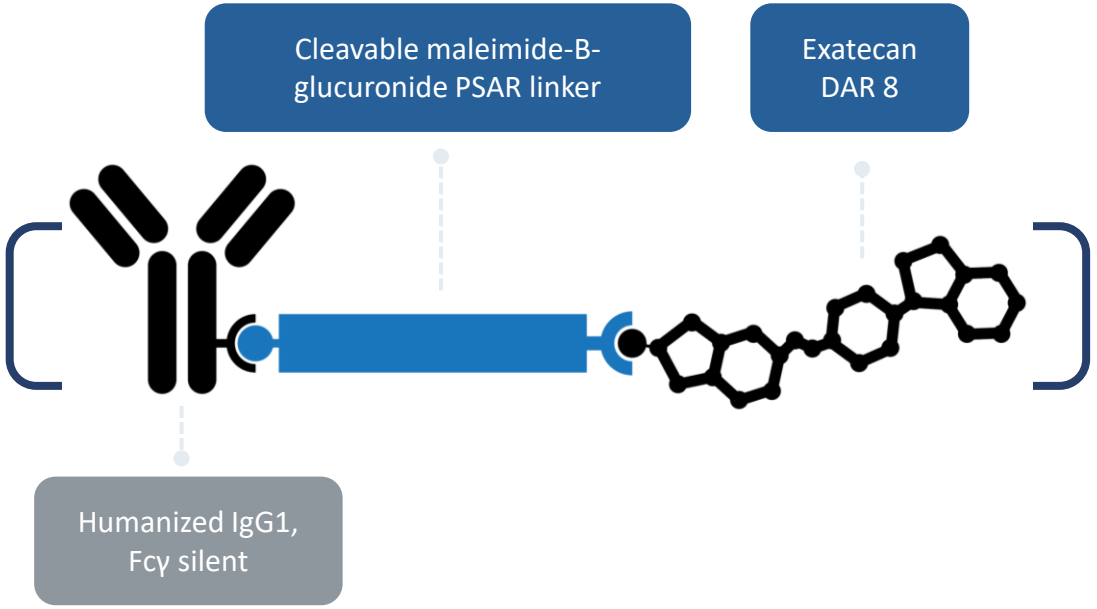
Program Background

- Improved linker-payload stability with homogeneous DAR 8[1,2]
- In preclinical studies, achieved significant tumor regression in MMAE-resistant models and across Nectin-4 expression levels[1,2]
- **LY4101174:** Phase I trial (EXCEED) ongoing
- **LY4052031:** Phase I trial (NEXUS-01) planned for Q2 2024

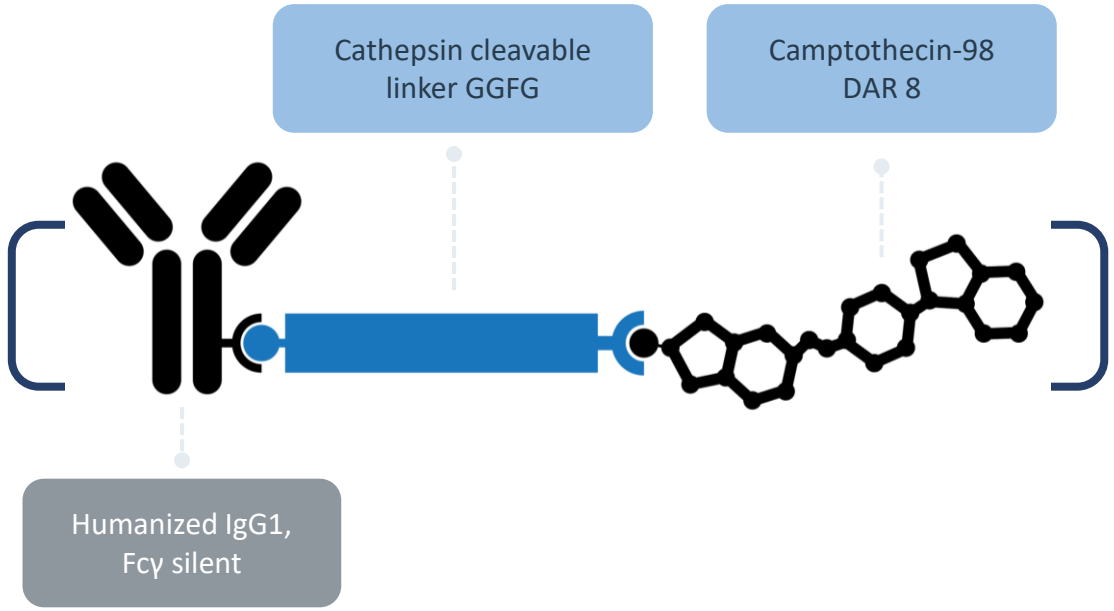
1. Data on file; 2. Fares J, et al. Presented at AACR-NCI-EORTC; October 11-15, 2023. ADC = antibody-drug conjugate; DAR = drug-to-antibody ratio; MMAE = monomethyl auristatin E.

Nectin-4 Targeted ADCs

LY4101174



LY4052031

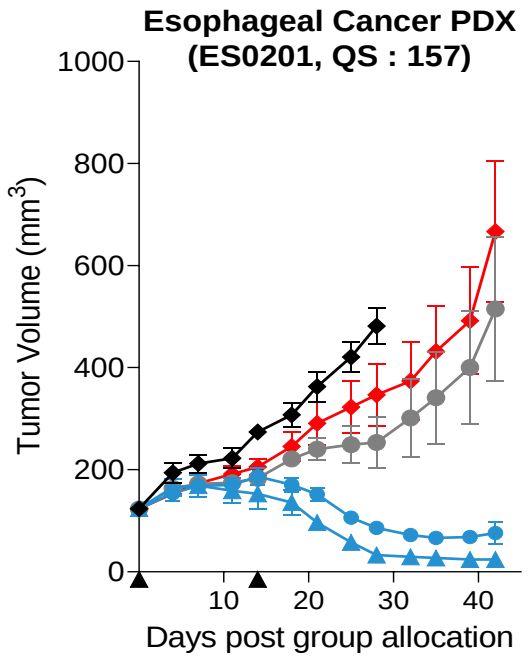


LY4101174 and LY4052031 each show preclinical activity in MMAE-resistant models

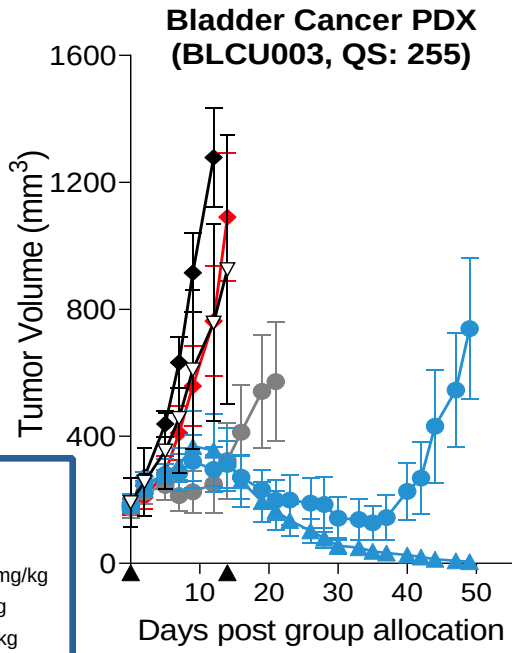
Fares J, et al. Presented at AACR-NCI-EORTC; October 11-15, 2023. IgG1 = immunoglobulin G 1; PSAR = polysarcosine.

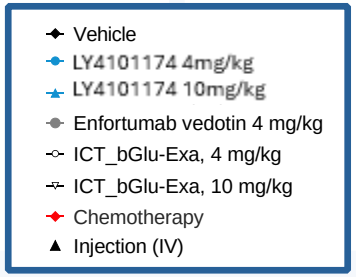
Nectin-4 ADCs: LY4101174

Low Nectin-4

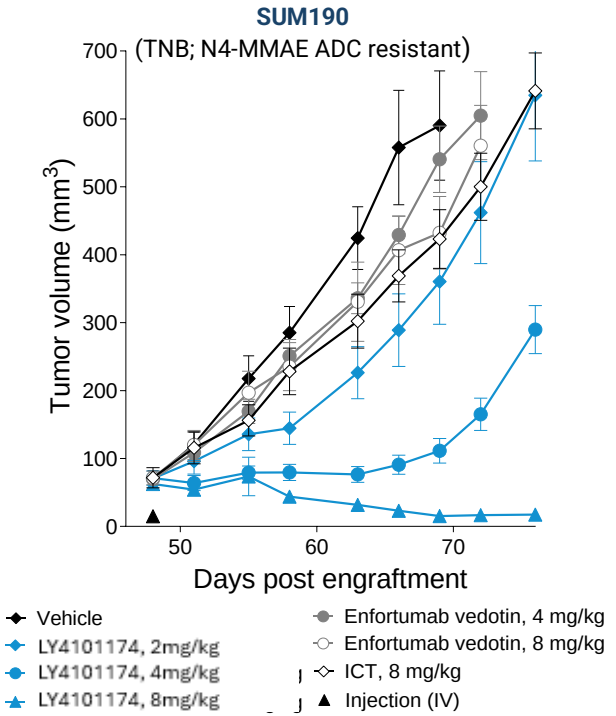


Moderate Nectin-4





Xenograft model with Nectin-4 MMAE ADC resistance



Drives tumor regression in multiple PDX models across Nectin-4 expression levels and is effective in Nectin-4 MMAE ADC-resistant preclinical models

Presented at AACR-NCI-EORTC; October 11-15, 2023. PDX = patient-derived xenograft.

SMARCA2 (BRM) Inhibitor

Barry Taylor, Ph.D.
Chief Scientific Officer

SMARCA2 (BRM) Inhibitor

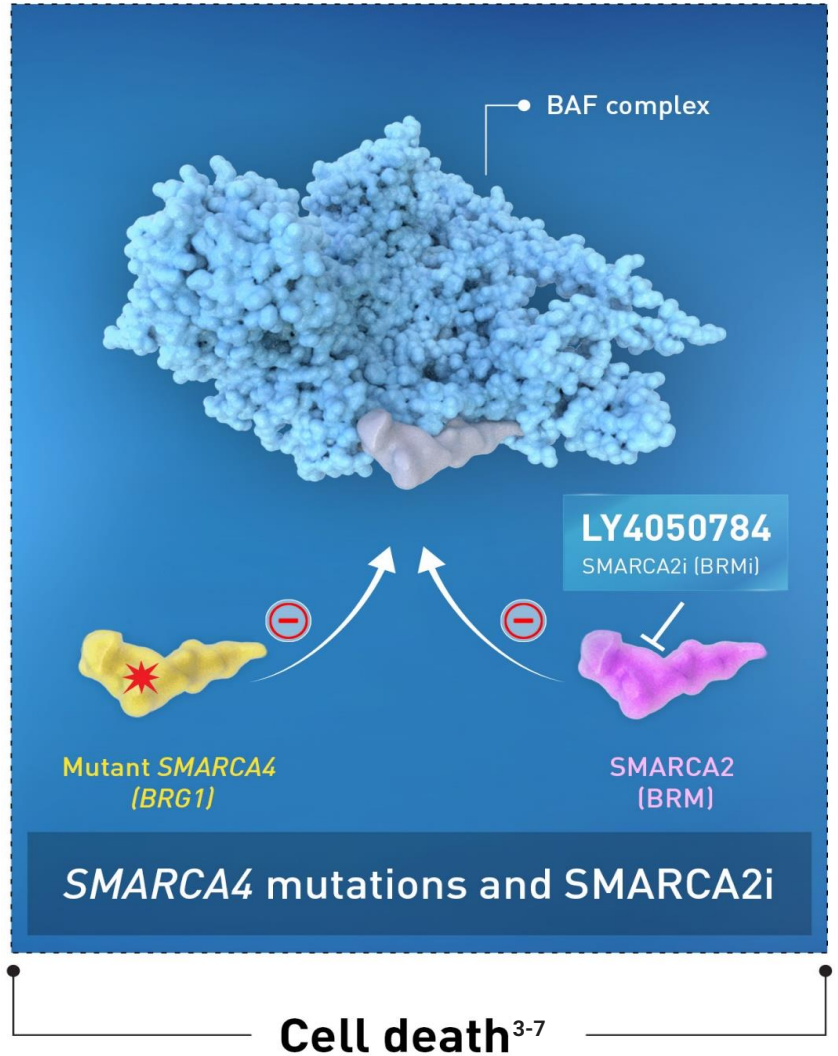
An orally bioavailable, potent and selective SMARCA2 (BRM) inhibitor

Current Treatment Landscape

- SMARCA4 mutations are associated with worse outcomes and present in 9%-11% of NSCLC[1,2]
- SMARCA4 and SMARCA2 are mutually exclusive ATPase subunits required for chromatin remodeling[3]

Program Thesis

- Develop a potential first-in-class potent and selective oral SMARCA2 inhibitor to achieve synthetic lethality in SMARCA4-deficient cancers



SMARCA4-mutant cancer cells are dependent on SMARCA2 ATPase for survival[5-8]

1. Dagogo-Jack I, et al. J Thorac Oncol. 2020;15:766-76; 2. Alessi JV, et al. J Thorac Oncol. 2021;16:1176-87; 3. Jancewicz I, et al. Epigenetics Chromatin. 2019;13:68; 4. Zhang B, et al. 2021; 5. Papillon JPN, et al. J Med Chem. 2018;61:10155-72; 6. Helming KC, et al. Cancer Cell. 2014;26:309-17; 7. Wilson BG, et al. Mol Cell Biol. 2014;34:1136-44; 8. Hoffman GR, et al. Proc Natl Acad Sci U S A. 2014;111:3128-33. NSCLC = non-small cell lung cancer.

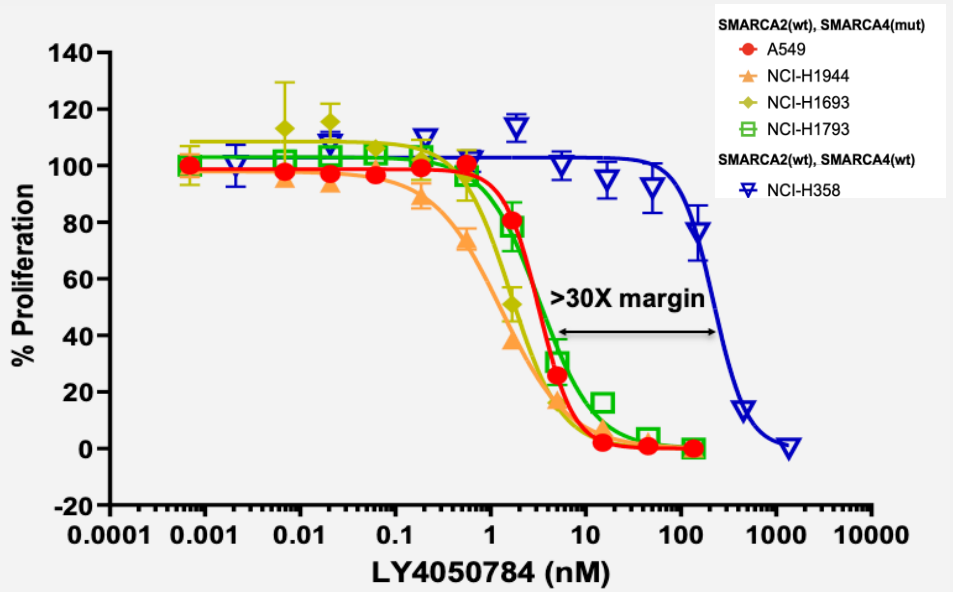
SMARCA2 (BRM) Inhibitor

An orally bioavailable, potent and selective SMARCA2 (BRM) inhibitor

Program Background

- Strategic collaboration with Foghorn Therapeutics to create novel oncology medicines, including Foghorn's selective SMARCA2 (BRM) program
- Selective oral SMARCA2 inhibitor with >30x margin for SMARCA2 vs SMARCA4
- Tumor regression and tumor growth arrest in preclinical models, including SMARCA-mutant cell lines containing KRAS, TP53, STK11, and KEAP1 mutations
- IND filing in Q2 2024

NSCLC in vitro proliferation assay



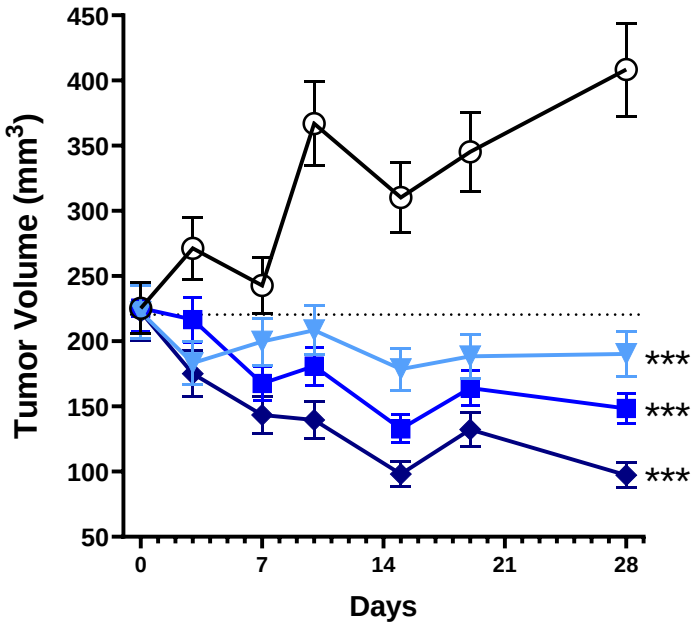
LY4050784 exhibits >30-fold increased potency against SMARCA2 (BRM) vs SMARCA4 (BRG1)

Lee J, et al. Presented at AACR; April 5-10, 2024.

IND = investigational new drug.

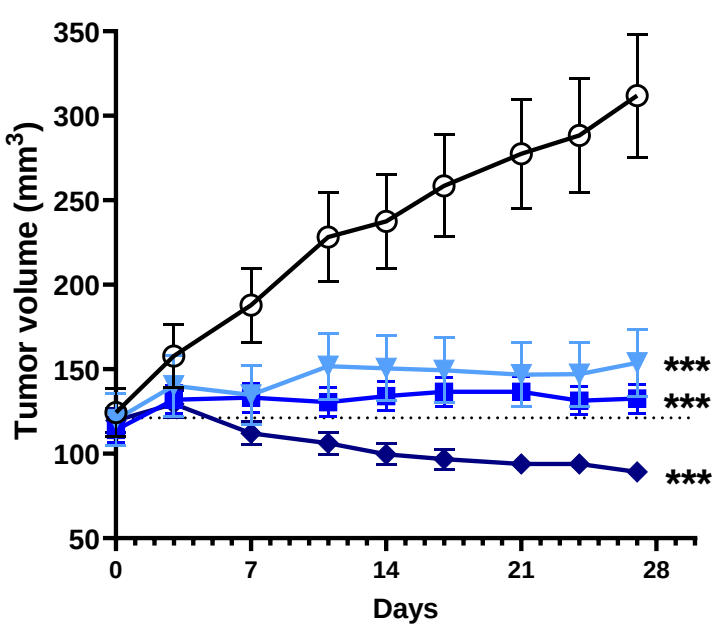
SMARCA2 (BRM) Inhibitor

NCI-H1793 (SMARCA4-mutant)



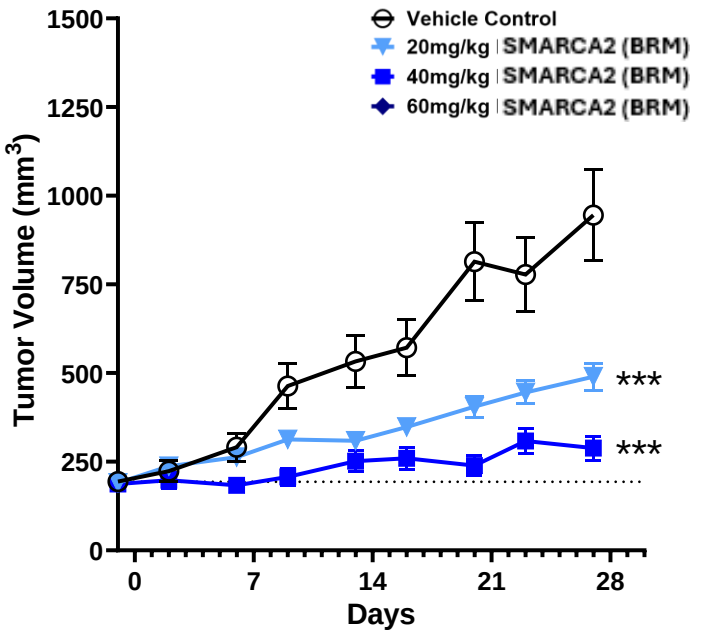
Mutational profile:
SMARCA4 E514*, TP53 R209* R273H, ARID1A C884*...

NCI-H2126 (SMARCA4-mutant)



Mutational Profile:
SMARCA4 W764R, TP53 E62*, STK11-/-, CDKN2A-/-, KEAP1 R272C...

A549 (SMARCA4 and KRAS G12S double mutant)



Mutational profile:
SMARCA4 Q729fs / H736Y, KRAS G12S, STK11-/-, CDKN2A-/- KEAP1 G333C...

Complete tumor growth inhibition or regression in all models tested

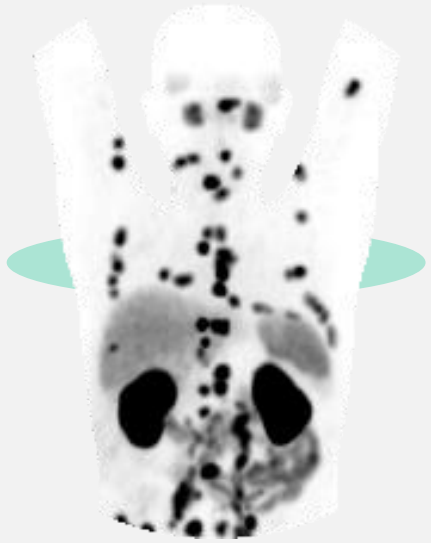
Lee J, et al. Presented at AACR; April 5-10, 2024.

Radioligand Therapy

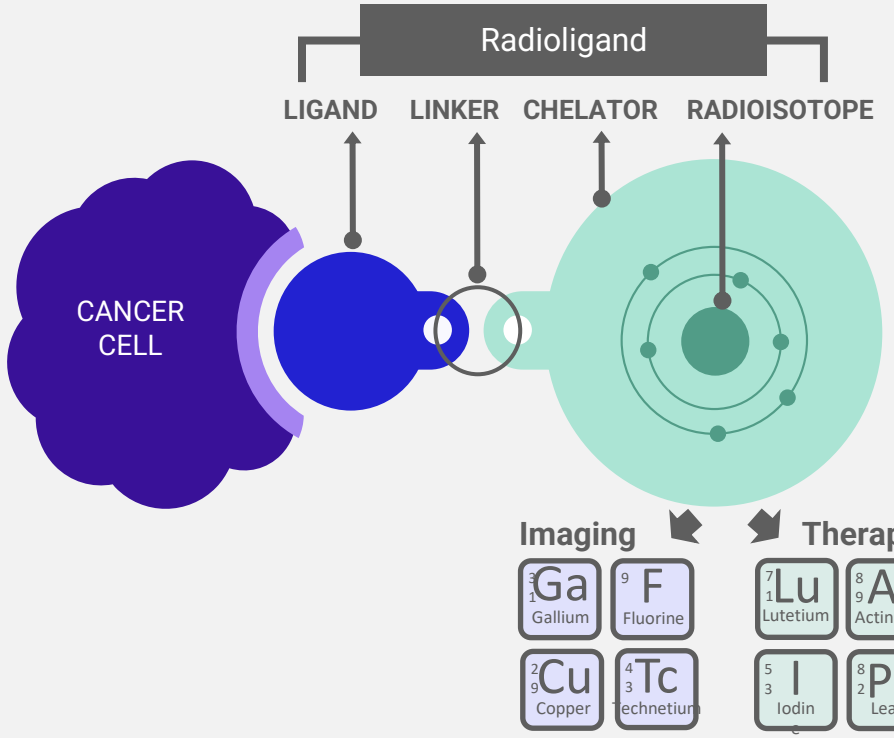
Theranostics Enable Us to Treat What We See with RLTs

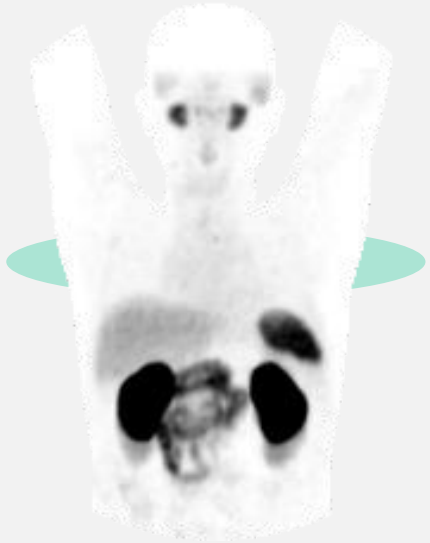
Next-generation radionuclides for paired imaging and treatment

PSMA overexpressed on prostate cancer cells + **PSMA-specific ligand seeks out cancer cells** + **The radioisotope emits ionizing radiation** = **Ionizing radiation kills tumor cell, while minimizing damage to healthy tissue**



PSMA-PET before treatment[1]





PSMA-PET after three ^{177}Lu-PSMA treatments[1]

1. Data on File. PET = positron emission tomography;
PSMA = prostate-specific membrane antigen; RLT = radioligand therapy.

^{225}Ac-PSMA-62

A Next-Generation PSMA Radioligand Optimized for Delivery of Ac-225

Current Treatment Landscape

- Despite advances in radioligand therapies, mCRPC remains a fatal condition
- Current-generation ^{225}Ac-PSMA causes significant off-tumor salivary toxicity

Program Thesis

- Improved ligand characteristics enable use of short-range, high LET alpha-emitter, Ac-225 in PSMA RLT

Program Background

- PSMA-62 improves preclinical affinity, internalization, and tumor uptake[1]
- High-energy alpha emissions from Ac-225 causes deadly double-strand DNA breaks
- Shorter tissue penetration of Ac-225 may optimize killing of micro-metastases while sparing normal tissues
- Phase I trial (ACCEL) ongoing

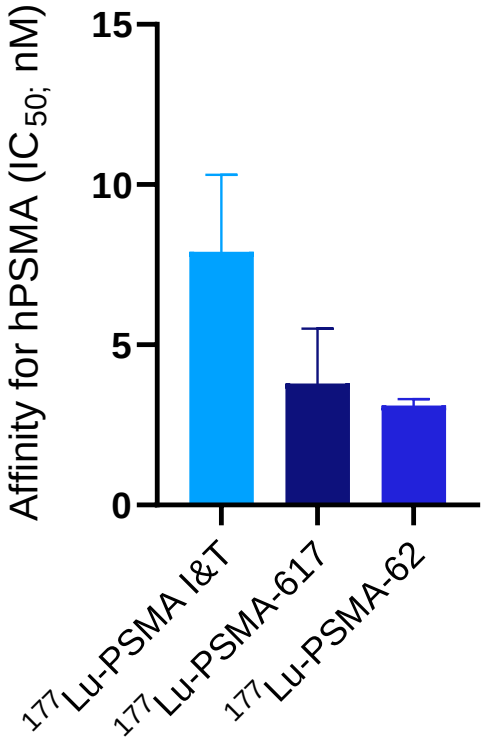
1. Vito A, et al. Presented at TAT Symposium; February 27 – March 2, 2023.

LET = linear energy transfer; mCRPC = metastatic castration-resistant prostate cancer.

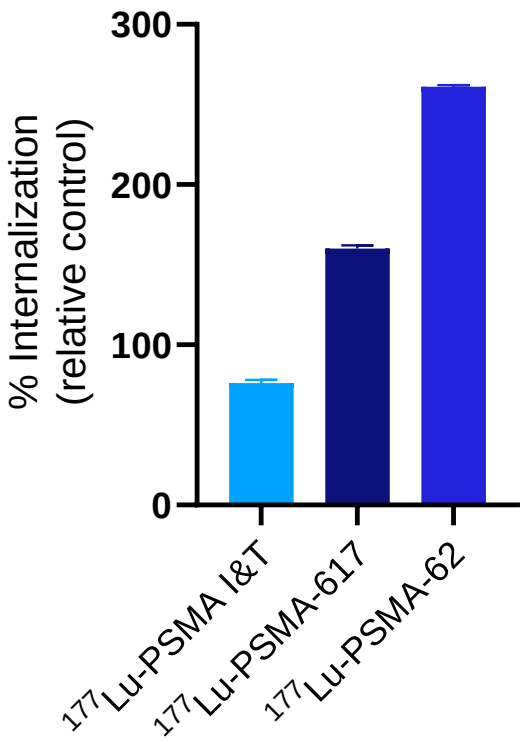
^{225}Ac-PSMA-62

A next-generation PSMA radioligand optimized for delivery of Ac-225

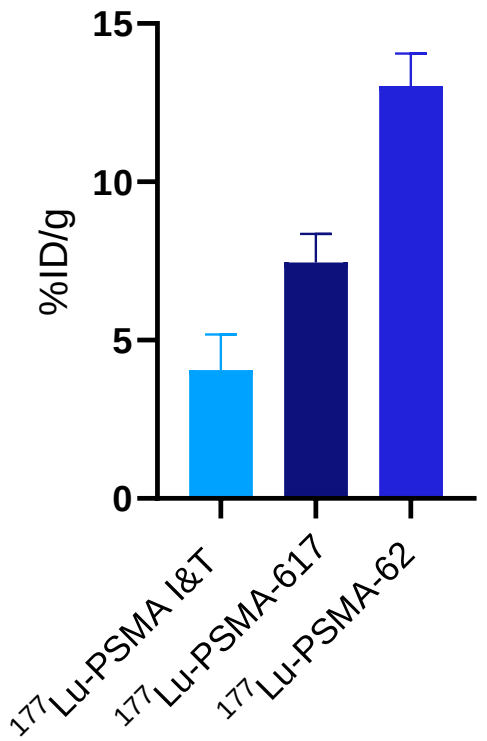
Improved Affinity



Improved Internalization



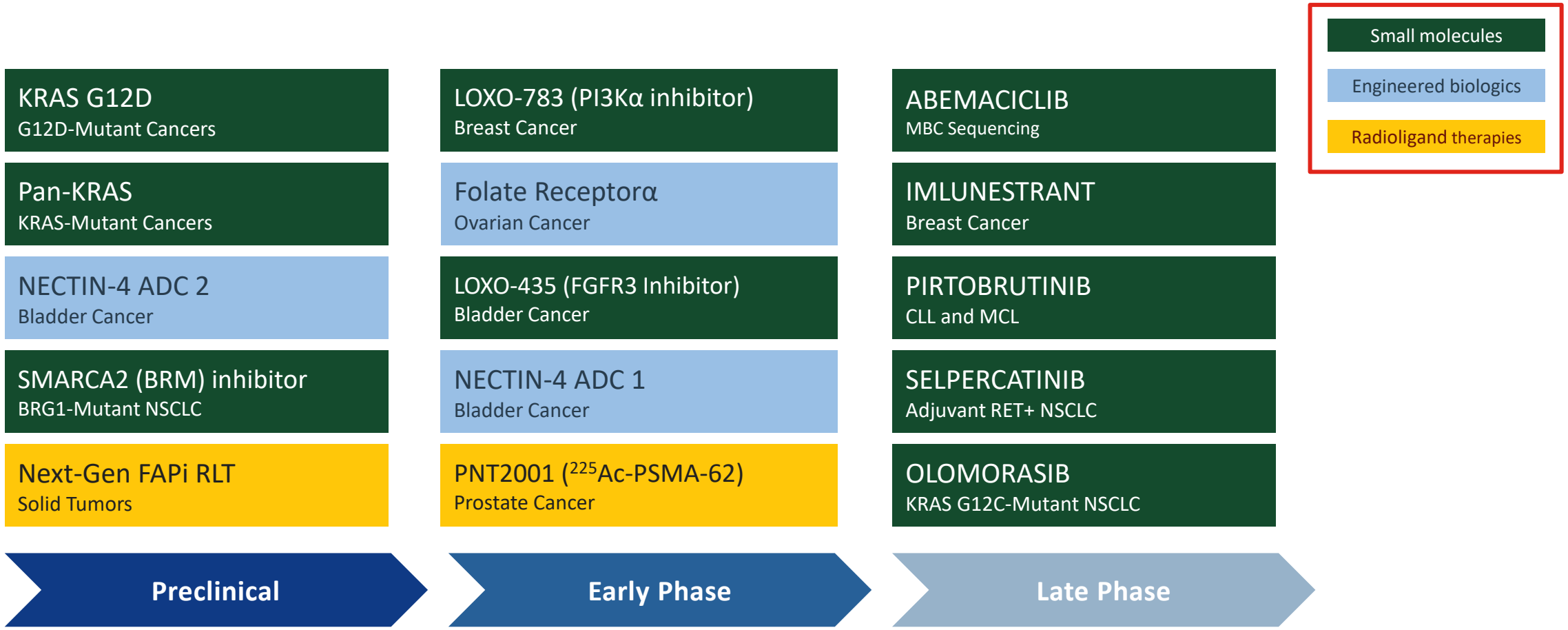
Improved Tumor Uptake



Linker technology allows for increased internalization into cells, resulting in increased tumor uptake

1. Vito A, et al. Presented at TAT Symposium; February 27 – March 2, 2023.

Select Publicly Disclosed Oncology Pipeline



ADC = antibody-drug conjugate; CLL = chronic lymphocytic leukemia; FAPi = fibroblast activation protein inhibitor; MBC = metastatic breast cancer; MCL = mantle cell lymphoma; NSCLC = non-small cell lung cancer; PSMA = prostate-specific membrane antigen; RLT = radioligand therapy.

Q&A Session

Q&A With The Lilly Oncology Leadership Team

Jake Van Naarden
President

Barry Taylor, Ph.D.
Chief Scientific Officer

Kara Clinton
Global Medical Affairs

Winselow Tucker
Chief Commercial Officer

Arjun Balar, M.D.
Global Clinical Development

Lillian Smyth, M.D.
Global Head, Breast Cancer

John Pagel, M.D., Ph.D.
Global Head, Hematology

Geoff Oxnard, M.D.
Global Head, Thoracic Cancer

Conclusions

Oncology at Lilly has a strong foundation but has undergone a transformation since 2019, with 2024 poised to be a productive year of new clinical starts

We are prosecuting programs across an increasingly diverse oncology pipeline in areas of high conviction biology and new innovation

With a robust clinical and preclinical pipeline, we are working to speed medicines to patients and increase our impact in oncology

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