Exelixis R&D Day:
Science & Strategy
Agenda

- Strategic Overview
- R&D for Commercial Impact
- Broadening Research Impact in Biotherapeutics & Small Molecules
- Break – 10 Minutes
- Zanzalintinib in Clear Cell RCC: Results from STELLAR-001
- Focused Execution Drives Long-term Value Creation
- Closing Remarks
- Break – 10 Minutes
- Q&A Session

*Lunch reception to follow the presentation next door in the foyer.*
Safe Harbor Statement

This presentation, including any oral presentation accompanying it, contains forward-looking statements, including, without limitation, statements related to: Exelixis’ belief it is positioned to be a global biotech leader in oncology R&D; Exelixis’ overall strategy and commitment to value creation in the short-, middle- and long-term horizon by helping more patients with cancer; potential new market opportunities for the cabozantinib franchise in mCPRC and NET, should Exelixis obtain regulatory approvals for cabozantinib in those indications; Exelixis’ commercial strategy to build oncology franchises across the GU, GI, Lung/H&N and GYN/breast core disease areas, and Exelixis’ belief that the breadth and depth of its pipeline is well-positioned to build on success in GU and GI while delivering growth in new disease areas; the commercial potential of zanablitinib, XB002, XL309 and the rest of the Exelixis pipeline, and Exelixis’ belief that a future multi-product portfolio could eventually treat up to 13 tumors and serve over ten times the current addressable patient population for cabozantinib; Exelixis’ drug discovery strategy to expand the pipeline with development candidates that have potential for differentiated clinical profiles, and Exelixis’ expectation it will build a consistent flow of development candidates and target two new INDs per year; Exelixis’ preclinical development plans for and beliefs regarding the therapeutic potential of its biotherapeutics development candidates, including XB010, XB628, XB371 and XB064, as well as its small molecule development candidates, including XL495 and EXEL-7871; Exelixis’ clinical development plans for and beliefs regarding the therapeutic potential of zanablitinib, XB002 and XL309; Exelixis’ plans for future data presentations, including from CONTACT-02, and Exelixis’ overall vision for development execution; and Exelixis’ anticipated long-term milestones to drive value creation in 2023, in 2024 through 2027, and in 2028 and beyond. Any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements and are based upon Exelixis’ current plans, assumptions, beliefs, expectations, estimates and projections. Forward-looking statements involve risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in the forward-looking statements as a result of these risks and uncertainties, which include, without limitation: the degree of market acceptance of CABOMETYX and other Exelixis products in the indications for which they are approved and in the territories where they are approved, and Exelixis’ and its partners’ ability to obtain or maintain coverage and reimbursement for these products; the effectiveness of CABOMETYX and other Exelixis products in comparison to competing products; the level of costs associated with Exelixis’ commercialization, research and development, in-licensing or acquisition of product candidates, and other activities; Exelixis’ ability to maintain and scale adequate sales, marketing, market access and product distribution capabilities for its products or to enter into and maintain agreements with third parties to do so; the availability of data at the referenced times; the potential failure of cabozantinib, zanablitinib and other Exelixis product candidates, both alone and in combination with other therapies, to demonstrate safety and/or efficacy in clinical testing; uncertainties inherent in the drug discovery and product development process; Exelixis’ ability to identify strategic opportunities to enhance its pipeline and to consummate the necessary transactions; Exelixis’ dependence on its relationships with its collaboration partners, including their pursuit of regulatory approvals for partnered compounds in new indications, their adherence to their obligations under relevant collaboration agreements and the level of their investment in the resources necessary to complete clinical trials or successfully commercialize partnered compounds in the territories where they are approved; complexities and the unpredictability of the regulatory review and approval processes in the U.S. and elsewhere; Exelixis’ continuing compliance with applicable legal and regulatory requirements; unexpected concerns that may arise as a result of the occurrence of adverse safety events or additional data analyses of clinical trials evaluating cabozantinib and other Exelixis product candidates; Exelixis’ dependence on third-party vendors for the development, manufacture and supply of its products and product candidates; Exelixis’ ability to protect its intellectual property rights; market competition, including the potential for competitors to obtain approval for generic versions of Exelixis’ marketed products; changes in economic and business conditions; and other factors detailed from time to time under the caption “Risk Factors” in Exelixis’ most recent Annual Report on Form 10-K and subsequent Quarterly Reports on Form 10-Q, and in Exelixis’ other future filings with the Securities and Exchange Commission (SEC). All forward-looking statements in this presentation are based on information available to Exelixis as of the date of this presentation, and Exelixis undertakes no obligation to update or revise any forward-looking statements contained herein, except as required by law.
Strategic Overview

Michael M. Morrissey, Ph.D.
President and CEO
EXEL 2024: Positioned to Be Global Biotech Leader in Oncology R&D

- Cabozantinib: Blockbuster VEGFR TKI franchise
- Deep pipeline targets 10x more patients than cabo
- Conviction to pursue differentiation in Phase 3
- Disciplined R&D efforts in line with revenue peers
- Urgency, focus & excellence define our work

EXEL R&D – Improve SOC for cancer patients with a pipeline of differentiated drugs

SOC = standard of care
TKI = tyrosine kinase inhibitor
Value Creation Driven By Singular Focus on Cancer Patients

1. Strong Returns from CABO
2. Focused Strategy
3. Innovative Pipeline
4. Big, Small Biotech Culture

R&D strategy in solid tumor oncology
Singular focus on improving standard of care for patients with cancer
Execute at the level of big pharma and with the agility of small biotech
Culture of collaboration – internal and external – maximizes impact and ROI

Exelixis is committed to creating value in the short-, mid- and long-term horizon by helping more patients with cancer

#1 launch in biotech oncology (2016)
54% sales* CAGR from 2016 – 2022
NET, mCRPC drives potential near-term growth in new indications

Robust pipeline of differentiated small molecule and biotherapeutics programs
Next generation clinical stage programs (ZANZA, XB002) drive mid-term growth

CAGR = compound annual growth rate
NET = neuroendocrine tumors
mCRPC = metastatic castration-resistant prostate cancer
ROI = return on investment

*Global net product revenue
Cabozantinib Franchise Success Provides Blueprint for Pipeline Strategy

Unique Target Profile
Targets MET, VEGFRs, TAMKs and other kinases implicated in tumor growth

Active in >20 Tumor Types
CRPC, breast cancer, urothelial cancer and others

6 Approvals, >20k Patients Treated per Quarter
Approved in MTC, DTC, RCC (3) and HCC

Superior Clinical Activity in RCC
Compared to sunitinib in head-to-head trials

Global “Blockbuster” Status
Net global revenues of ~$2.2B (LTM)

#1 TKI in aRCC
#1 TKI + IO Combination in 1L aRCC

Cabozantinib’s clinical and commercial success achieved by improving SOC for cancer patients

CRPC = castration-resistant prostate cancer
MTC = medullary thyroid cancer
DTC = differentiated thyroid cancer
aRCC = advanced renal cell carcinoma
HCC = hepatocellular carcinoma
TKI = tyrosine kinase inhibitor
SOC = standard of care
LTM = last twelve months
OS = overall survival
Commercial Success Results from Disciplined R&D Investments

**Cabozantinib Pivotal Trials, with 14 Trials Read Out**
- 14 of 17 trials focused on GU & GI cancers

**Pivotal Trials with Positive Primary Endpoint**
- vs. Industry Average of 53%\(^1\)

**VEGFR TKI Launched* in VEGFR TKI Sales**
- 8\(^{th}\) place
- #1

---

*In the U.S.
\(^1\) Trialtrrove Analysis of Solid Tumor Phase 3 Trials Jan 2013 – Nov 2023 (n = 461 trials)

GU = Genitourinary
GI = Gastrointestinal
TKI = tyrosine kinase inhibitor
Collaborate to Succeed: Risk-Sharing Maximizes Optionality & Impact

<table>
<thead>
<tr>
<th>Combination</th>
<th>Phase 3 Study</th>
<th>Partners</th>
<th>Commercial Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib + Nivolumab</td>
<td><strong>CheckMate -9ER</strong> 1L aRCC</td>
<td>Bristol Myers Squibb, Ipsen, Takeda</td>
<td>Doubling of cabozantinib franchise global annual net product revenue from ~$1B in 2020 to ~$1.9B in 2022</td>
</tr>
<tr>
<td>Cabozantinib + Atezolizumab</td>
<td><strong>CONTACT-01</strong> NSCLC, <strong>CONTACT-02</strong> mCRPC, <strong>CONTACT-03</strong> RCC</td>
<td>Roche, Ipsen, Takeda</td>
<td>Positive results from <strong>CONTACT-02</strong> announced</td>
</tr>
</tbody>
</table>

Pursuing similar risk-sharing collaborations for zanza and other pipeline programs enables the development of novel combinations to meaningfully improve SOC for patients

| ~25% Study Costs Funded by Exelixis |

1L = first-line  
aRCC = advanced renal cell carcinoma  
NSCLC = non-small cell lung cancer  
mCRPC = metastatic castration-resistant prostate cancer  
SOC = standard of care

1 Exelixis JPM Presentation, Jan 2020
End-to-End Integration of Research, Development and Commercial

- **Multi-modal approach** to reduce target/biology risk
- Prioritization of programs with potential for clinical differentiation

- Balance the optimization of probability of success, speed and value across pipeline
- Novel combinations in earlier lines
- Efficiency in execution

- Maximize patient impact in large solid tumor populations
- Strong & early focus on competitive differentiation

Integration of R&D with commercial provides a complementary and balanced approach to driving science & strategy
# Exelixis Biotherapeutics & Small Molecule Pipeline

## Pre-IND
- XB010: 5T4-MMAE
- XB628: PD-L1-NKG2A
- XB371: TF-TOPOi
- XL495: PKMYT1
- XB064: ILT2

## Phase 1
- XB002: TF-MTI
- XL309: USP-1
- ADU-1805: SIRPα
- CBX-12: TOPOi PDC

## Phase 1b/2
- Zanzalintinib: MET/VEGFR/AXL
  - Multiple solid tumors
- XB002: TF-MTI
  - Multiple solid tumors

## Pivotal
- Zanzalintinib: 3L+ CRC
- Zanzalintinib: nccRCC
- Zanzalintinib: SCCHN

## 2023 Discontinuations
- XB014: PD-L1-CD47 (PC)
- XL114: FABP5 (Ph1)
- XL102: CDK7 (Ph1)

## Drug Modality
- Small Molecule
- Monoclonal Antibody
- Bispecific Antibody
- Antibody/Peptide Drug Conjugate

## Combination Partner
- PD-L1
- Novel ICI (e.g., LAG-3, TIGIT)
- Other (e.g., VEGF, HIF2α)

---

**Abbreviations:**
- MMAE = monomethyl auristatin E
- TF = tissue factor
- 5T4 = programmed death-ligand 1
- NKG2A = natural killer cell receptor group 2A
- USP-1 = ubiquitin specific peptidase 1
- PKMYT1 = protein kinase membrane associated tyrosine/threonine 1
- CD47 = cluster of differentiation 47
- LAG-3 = lymphocyte activation gene 3
- CDK7 = cyclin-dependent kinase 7
- ICI = immune checkpoint inhibitor
- HIF2α = hypoxia-inducible factor 2 α
Strategic Vision for Building Multiple Franchises Across Portfolio

"ALL IN" Product Development Strategy

Prioritize Programs with Compelling Emerging Clinical Data

Collaborate with Competitors

Improve SOC with Differentiated Drugs and Novel Combinations

Maximize speed and impact of development and commercialization activities for zanzalintinib, XB002, XL309 and rest of pipeline
Today’s Speakers

PJ Haley
EVP, Commercial
• R&D for Commercial Impact

Dana T. Aftab, Ph.D.
EVP, Discovery & Translational Research and CSO
• Broadening Research Impact in Biotherapeutics & Small Molecules

Sumanta Pal, M.D., FASCO
Professor, Department of Medical Oncology & Therapeutics Research, City of Hope Cancer Center
• Zanzalintinib in Clear Cell RCC: Results from STELLAR-001

Amy Peterson, M.D.
EVP, Product Development & Medical Affairs and CMO
• Focused Execution Drives Long-term Value Creation

RCC = renal cell carcinoma
R&D for Commercial Impact

PJ Haley
EVP, Commercial
Pipeline Commercial Focus Through the Cabo Lens

**Cabozantinib Lens**

- **$2.2B** in Global Net Product Revenue (2023 LTM)
- **#1 TKI** in aRCC and 2L HCC – tumors with multiple TKIs approved
- **#1 TKI + IO** in 1L aRCC – multiple TKI + IO combinations marketed; approved 20 months after pembrolizumab + axitinib

**Pipeline Focus**

- **Solid Tumor Focus**: address unmet need that exists across solid tumors and stay on the forefront of evolving landscapes
- **Maximize Patient Impact**: advance standard of care to move the needle for large patient populations
- **Best-in-class Target Product Profiles**: clinical differentiation drives commercial success, even in competitive markets

**Abbreviations**

- **1L** = first-line
- **2L** = second-line
- **LTM** = last twelve months
- **TKI** = tyrosine kinase inhibitor
- **aRCC** = advanced renal cell carcinoma
- **HCC** = hepatocellular carcinoma
- **IO** = immunotherapy
### Potential New Market Opportunity: mCRPC

<table>
<thead>
<tr>
<th>2023 Estimated Drug-Treatable Incidence:</th>
<th>Current Therapeutic Options:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1L: ~33k</strong></td>
<td>▪ NHT</td>
</tr>
<tr>
<td></td>
<td>▪ Docetaxel</td>
</tr>
<tr>
<td><strong>2L: ~26k</strong></td>
<td>▪ NHT</td>
</tr>
<tr>
<td></td>
<td>▪ Docetaxel</td>
</tr>
<tr>
<td><strong>3L+: ~18k</strong></td>
<td>▪ JEVTANA</td>
</tr>
<tr>
<td></td>
<td>▪ PLUVICTO</td>
</tr>
<tr>
<td></td>
<td>▪ Docetaxel</td>
</tr>
</tbody>
</table>

#### Cabozantinib Opportunity in mCRPC

- Low 5-year survival rate of 15%
- Majority of mCRPC patients are NHT-experienced:
  - 1L: >50% patients, 2L: almost all patients
- Significant need for chemotherapy free treatment options for patients progressing from NHTs
- Excitement for new mechanisms of action in mCRPC
- If approved, cabozantinib + atezolizumab represents a compelling option for patients who have progressed from NHT and want to delay chemotherapy
- Synergy with existing commercial infrastructure and customers

---

1L = first-line | mCRPC = metastatic castration-resistant prostate cancer | IO = immunotherapy
2L = second-line | NHT = novel hormonal therapy | TKI = tyrosine kinase inhibitor
3L = third-line | Sources: Estimated drug-treatable incidence (2024): DRG, 10/2023; Post-novel hormonal therapy: BrandImpact, July 2023
Potential New Market Opportunity: NET

Neuroendocrine tumors are a heterogeneous group of malignancies generally considered to be indolent.

NETs represent a significant prevalent population (>5x incidence), as most patients progress through multiple lines of therapy.

Increasing incidence with improved detection.

Significant opportunity exists, as patients have limited treatment options.

Cabozantinib potentially represents a treatment option for all previously treated NET patients, regardless of tumor location and SSTR status.

Potential to be a new standard of care in 2L+ neuroendocrine tumors.
Strengthen Leadership and Innovation in Exelixis Current Disease Areas

1. Strengthen leadership in RCC through expansive development of zan扎linib
   Expand presence in genitourinary & gastrointestinal cancers through development in new indications and combinations

2. Expand into New Disease Areas Using Our Strengths as a Guide
   Establish foothold in head & neck and non-small cell lung cancers through zan扎linib and XB002
   Leverage diverse pipeline to develop the right treatment approaches for patients who will benefit the most

GU = genitourinary cancers
GI = gastrointestinal cancers
H&N = head & neck cancers
GYN = gynecological cancers
RCC = renal cell carcinoma

Maximize patient impact and chance of success in solid tumor oncology
Portfolio Planning Maximizes Value and Drives Focus

Portfolio Prioritization Through the Lens of Patient Impact and Chance of Success

- Market Size
- Unmet Need
- Competitive Landscape

Patient Impact
- High
- Low

Chance of Success
- High
- Low

- Clinical Proof of Concept
- Development/Regulatory Risk

- Develop data to de-risk
- Prioritize development to maximize value
- Deprioritize
- Identify opportunities for quick wins

Disease Areas/Tumors of Interest

- Genitourinary
  - Kidney, Prostate
  - ~100k
- Gastrointestinal
  - Liver, Colorectal, Pancreatic
  - ~220k
- Lung/H&N
  - Non small cell lung, Head & neck
  - ~330k
- Gynecological/Breast
  - Endometrial, Breast
  - ~140k

Addressable Patients (US)*

*2023 Drug treatable patients across lines of therapy in the advanced/metastatic setting. Source: DRG
Pipeline Is Well Positioned to Build on Success in GU and GI, while Delivering Growth in New Disease Areas

<table>
<thead>
<tr>
<th>Priority Tumors</th>
<th>Genitourinary</th>
<th>Gastrointestinal</th>
<th>Lung/H&amp;N</th>
<th>Gynecological/Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCC</td>
<td>X</td>
<td>Zanza</td>
<td>Zanza</td>
<td>Zanza</td>
</tr>
<tr>
<td>Prostate</td>
<td>X</td>
<td>Zanza</td>
<td>Zanza</td>
<td>Zanza</td>
</tr>
<tr>
<td>HCC</td>
<td>X</td>
<td>Zanza</td>
<td>Zanza</td>
<td>Zanza</td>
</tr>
<tr>
<td>Colorectal</td>
<td>X</td>
<td>Zanza</td>
<td>Zanza</td>
<td>Zanza</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>X</td>
<td>Zanza</td>
<td>Zanza</td>
<td>Zanza</td>
</tr>
<tr>
<td>NSCLC</td>
<td>X</td>
<td>Zanza</td>
<td>Zanza</td>
<td>Zanza</td>
</tr>
<tr>
<td>Head &amp; Neck (H&amp;N)</td>
<td>X</td>
<td>Zanza</td>
<td>Zanza</td>
<td>Zanza</td>
</tr>
</tbody>
</table>

Key EXEL Programs

- **TKI**: Zanza
- **Synthetic Lethality**
  - XL309
  - XL495
- **ADCs**
  - XB002
  - XB010
  - XB371
- **IO**
  - XB628
  - XB064

Develop internal combinations and forge external collaborations to develop novel and best-in-class combinations across disease areas

*2023 drug treatable patients across lines of therapy in the advanced/metastatic setting. Source: DRG

---

GU = genitourinary cancers
GI = gastrointestinal cancers
RCC = renal cell carcinoma
HCC = hepatocellular carcinoma
NSCLC = non-small cell lung cancer
TKI = tyrosine kinase inhibitor
ADC = antibody-drug conjugate
IO = immunotherapy
H&N = head & neck
Zanzalintinib: VEGFR TKI Combination Partner of Choice

**Strategic Focus**
1. **Accelerate development** in high unmet need indications
2. **Expand TKI footprint** in indications where IO is approved
3. **Develop new standards of care** in novel combinations

**Competitive Differentiation**
+ Favorable benefit/risk profile vs. other VEGFR TKIs
+ Builds on Cabo’s key drivers of commercial success
+ VEGFR TKI combination partner of choice

**Commercial Potential**
- **Addressable Pts (US)**
  - ~31k 3L+ CRC
  - ~13k 1L SCCHN (PD-L1+)
  - ~7k nccRCC

**Commercial Drivers for Zanza**
- Large market with high unmet need
- Opportunity in both NLM & LM
- First industry-sponsored RCT in ncc
- Continued commitment to RCC
- Similar market size to RCC
- Limited advancements in SOC

**Disease Areas of Interest:**
- GU
- GI
- Lung/H&N
- GYN/Breast

<table>
<thead>
<tr>
<th>TKI</th>
<th>RCC</th>
<th>NLM</th>
<th>LM</th>
<th>IO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrosine kinase inhibitor</td>
<td>Renal cell carcinoma</td>
<td>Non-liver metastases</td>
<td>Liver metastases</td>
<td>Immunotherapy</td>
</tr>
<tr>
<td>SCCN</td>
<td>Head &amp; neck squamous cell carcinoma</td>
<td>Non-clear cell RCC</td>
<td>Colorectal cancer</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GYN/Breast</td>
<td>Gynecological cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


*Clarivate DRG drug-treatable patients (2023) in the advanced/metastatic setting*
XB002 & XB371: Best-in-class Tissue-Factor (TF) ADC Franchise

**Strategic Focus**
1. Leverage differentiated profiles to improve outcomes and compete effectively
2. Accelerate development in markets with FIC potential
3. Access new indications with XB371 (TOPO1i payload)

**Competitive Differentiation**
- **XB002**: Potentially best-in-class safety and efficacy
- **XB371**: First-in-class Tissue Factor (TF) TOPO1i ADC

**Disease Areas of Interest:**
- **GU** ✓
- **GI** ✓
- **Lung/H&N** ✓
- **GYN/Breast** ✓

**Commercial Potential**
Tissue Factor ADC Franchise leverages a complementary approach to maximize optionality and drive value for patients

### XB002
- Head & Neck
- Prostate
- TNBC
- Cervical

### XB371
- NSCLC
- Endometrial
- Pancreatic
- Ovarian
- HR+ Breast
- Esophageal
- CRC
- SCLC

---

*Clarivate DRG drug-treatable patients (2023) in the advanced/metastatic setting across specified tumors*
XL309: Best-in-class USP1i with Potential to Build and Expand on PARPi

**Strategic Focus**

1. **Accelerate development** in PARPi-refractory patients
2. **Advance standard of care** in combination with PARPi
3. **Expand** beyond existing PARPi market

**Competitive Differentiation**

+ **Potentially differentiated safety profile** vs. competition
+ **Improved combinability** with PARPi, chemo and internal & external synthetic lethality targeting programs

**Initial Disease Areas of Interest:**

- **GU**
- **GI**
- **Lung/H&N**
- **GYN/Breast**

**Commercial Potential**

XL309 Has the Potential to Build and Expand Upon the Existing Attractive PARP Inhibitor Market

<table>
<thead>
<tr>
<th>PARPi Approved Tumors</th>
<th>Mutation Rate^</th>
<th>Addressable Pts (US)*</th>
<th>2022 PARPi US Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian</td>
<td>HRD+ ~50%</td>
<td>~20k</td>
<td>&gt;$1.6B</td>
</tr>
<tr>
<td>Breast</td>
<td>gBRCAm ~10%</td>
<td>~40k</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>HRRm ~30%</td>
<td>~21k</td>
<td></td>
</tr>
</tbody>
</table>

*Clarivate DRG drug-treatable patients (2023) in the advanced/metastatic setting

# Exelixis Commercial Vision: Multi-Product, Multi-Modal Solid Tumor Portfolio

## Patient Impact

<table>
<thead>
<tr>
<th>Year</th>
<th>Cabozantinib</th>
<th>Zanzalintinib</th>
<th>Balanced Portfolio with Broad Patient Impact Across Solid Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2023</td>
<td>RCC/HCC/DTC</td>
<td>CABO</td>
<td>EXEL-7871, XL495, XL309, Zanzalintinib, Cabozantinib, Zanzalintinib, Cabozantinib</td>
</tr>
<tr>
<td>2024-2027</td>
<td>RCC/HCC/DTC</td>
<td>XBO02</td>
<td>XB064, XB371, XB628, XB010, Zanzalintinib, Cabozantinib, Zanzalintinib, Cabozantinib</td>
</tr>
<tr>
<td>2028+</td>
<td>RCC/HCC/DTC</td>
<td></td>
<td>XB002, XB002</td>
</tr>
</tbody>
</table>

## Exelixis Commercial Vision

**Multi-Product, Multi-Modal Solid Tumor Portfolio**

### Maximize Cabo LCM to Fuel Clinical Pipeline Expansion

- **Small Molecule**
- **Biotherapeutic**

### Expand Beyond Cabo with Zanza and XB002

- Zanzalintinib
  - CRC/nccRCC
- Cabozantinib
  - CRPC/NET
- Cabozantinib
  - RCC/HCC/DTC

### Balanced Portfolio with Broad Patient Impact Across Solid Tumors

- EXEL-7871
- XL495
- XL309
- Zanzalintinib
  - H&N/++
- Cabozantinib
  - CRPC/NET
- Cabozantinib
  - RCC/HCC/DTC
- PB064
- XB371
- XB628
- XB010
- XB002

---

**Abbreviations:**
- RCC = renal cell carcinoma
- HCC = hepatocellular carcinoma
- DTC = differentiated thyroid cancer
- CRC = colorectal cancer
- NET = neuroendocrine tumors
- H&N = head & neck
- CRPC = castration-resistant prostate cancer
- nccRCC = non-clear cell renal cell carcinoma
- LCM = life-cycle management
Exelixis R&D Strategy Enables Us to Deliver on Our Mission

Multiple franchises across solid tumors with significant potential to improve the lives of cancer patients

RCC = renal cell carcinoma
HCC = hepatocellular carcinoma
DTC = differentiated thyroid cancer
CRC = colorectal cancer
NET = neuroendocrine tumors
H&N = head & neck
GYN = gynecologic tumors
GI = gastrointestinal tumors
GU = genitourinary tumors
TKI = tyrosine kinase inhibitor
TF = tissue factor

*Not yet approved
^2023 drug treatable patients in indications/tumors of interest across lines of therapy in the advanced/metastatic setting. Source: DRG
Broadening Research Impact in Biotherapeutics & Small Molecules

Dana T. Aftab, Ph.D.
EVP, Discovery & Translational Research and CSO
Pipeline Discovery: Focus through the Cabozantinib Lens

**Pipeline Focus**

- **Expand pipeline** with development candidates that have potential for **differentiated clinical profiles**
- **Biotherapeutics strategy:** focus on next-generation ADCs, monoclonal antibodies and bispecifics
- **Small molecule strategy:** focus on synthetic lethality and the tumor microenvironment

**Cabozantinib Lens**

- **Leveraging learnings & expertise** in drug discovery and development to design **next-generation compounds**
- **Deep focus on tumor biology** drives drug design strategy
- **Broadly applicable** drug candidates with activity across **multiple tumor types**
Discovering Next Generation Molecules with Best-In-Class Potential

Biology-Centric, Modality-Agnostic R&D

- Select High Impact Targets
- Small Molecule or Biotherapeutic?
- Learn from Competitors
- Apply Contemporary Technologies to Improve Development Candidates
- Empirically Determine the Right Combination of Factors

- Genitourinary
- Gastrointestinal
- Lung/Head & Neck
- Gynecological/Breast
Collaborative Platforms Enable Rapid Biotherapeutics Discovery

**Exelixis Expertise**

- Scientific leadership
- Project management
- Specialized lab functions

**Platforms / Technologies**

- **Catalent**
  - SMARTag® (ADCs)
- **invenra**
  - B-Body® (bispecifics)
- **ADAGENE**
  - SAFEbody® (masking)
- **NBE therapeutics**
  - SMAC-Technology™ (ADCs)
- **Ajinomoto**
  - AJICAP® (ADCs)

**Payloads**

- Auristatins
- TOPO1 inhibitors
- STING agonists
- Anthracyclines

**Antibody Discovery**

- **invenra**
- WuXi Biologics
- **GAMMA PHARMA**

**Scalable model - maximizes optionality, innovation and speed**
Technologies Drive Differentiated Approaches in Small Molecule Discovery

High-resolution structures solved at project initiation – yield vectors for design of more selective/potent molecules

CryoEM Structure of Chimeric Degrader Bound to KRAS + E3 Ligase

X-ray Crystal Structure of Inhibitor Bound to PKMYT1 (1.43 Å)

Rapid library construction enables a multiplexed approach to optimize potency, selectivity and properties

Electrophile

1st Iteration

2nd Iteration

Building Blocks

Library

Reaction in plates

Screening

Multiple Assays

Hits

QC Resyn

1st Iteration Hits

2nd Iteration Hits

Optimize

CryoEM = cryogenic electron microscopy
PKMYT1 = protein kinase membrane associated tyrosine/threonine 1
QC = quality control
Modality-Agnostic Discovery Strategy: Focus on Differentiation

**Small Molecules**
- XL495: PKMYT1
- XL309: USP1
- EXEL-7871: PLK4
- Synaptic Lethality
- Immuno-oncology
- Immune environment
- Antibody Drug Conjugates
- Biology-Centric, Modality-Agnostic R&D
- Clinical Program

**Bio-therapeutics**
- XB02: TF-MTI
- XB371: TF-TOPOi
- XB010: 5T4-MMAE
- XB628: PD-L1-NKG2A
- XB064: ILT-2

**Genitourinary**
- Usp1

**Gastrointestinal**
- PKMYT1

**Lung/Head & Neck**
- USP1 = ubiquitin specific peptidase 1
- PKMYT1 = protein kinase membrane associated tyrosine/threonine 1
- MTI = auristatin-based microtubulin inhibitor
- MMAE = monomethyl auristatin E
- PLK4 = polo-like kinase 4
- PD-L1 = programmed death-ligand 1
- ILT-2 = ILT2 = Ig-like transcript 2
- TOPOi = topoisomerase inhibitor
- NKGA = natural killer cell receptor group 2A
Productive Discovery Engine Has Created a Deep IND Pipeline

2024

- XB010: 5T4-MMAE
- XL495: PKMYT1
- XB628: PD-L1-NKG2A

2025

- XB371: TF-TOPOi
- XB064: ILT2
- EXEL-7871: PLK4

Drug Modality

- Small Molecule
- Bispecific Antibody
- Monoclonal Antibody
- Antibody Drug Conjugate

Consistent flow of development candidates targeting 2 INDs/year

Generating portfolio of molecules, all with potential for clinical differentiation
Biotherapeutics Pipeline
Biotherapeutics with Potential for Differentiating Clinical Activity

**XB010**
- 5T4-MMAE ADC, DAR = 2
- High expression in breast/GYN and lung/H&N tumors

**XB628**
- PD-L1 + NKG2A bispecific antibody
- Blocks inhibition of NK cell activation by tumor HLA-E, while relieving PD-L1 mediated T-cell checkpoint
- Acts as NK cell engager

**XB371**
- TF-TOPOi ADC, DAR = 8
- Broadens reach of TF franchise beyond XB002 to include tumors not responsive to tubulin inhibitors

**XB064**
- ILT2 monoclonal antibody
- Blocks inhibition of T-cells, macrophages, and NK cells by tumor HLA-G
- Associated with resistance to PD-1/L1 inhibitors
5T4 is an Optimal Target for an Antibody-Drug Conjugate Approach

5T4 is overexpressed in several cancer types with limited expression in normal adult tissues

**Function**
- 5T4 is associated with cancer stem cells (CSCs), cell adhesion, epithelial-to-mesenchymal transition, and pathways that promote CSC mobilization

**Healthy Adult Tissue Expression Profile**
- Syncytiotrophoblast membrane in normal placenta

**Solid Tumor Tissue Expression Profile**
- Breast, lung, endometrial, head and neck, cervical, and others
- Expression seen by immunohistochemistry in ~50% of circulating tumor cells in NSCLC patients

### 5T4 Expression & Anti-Tubulin Sensitivity

<table>
<thead>
<tr>
<th>Healthy Adult Tissue Expression Profile</th>
<th>5T4 Expression¹</th>
<th>Anti-Tubulin Sensitivity²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncytiotrophoblast membrane in normal placenta</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

**5T4 Expression & Anti-Tubulin Sensitivity**

- Mesothelioma
- Breast
- Lung
- Endometrial
- Head and neck
- Cervical
- Bladder
- Pancreatic
- Gastric
- Ovarian
- Colorectal
- Kidney
- Prostate

1 Exelixis IHC data; composite score based on percentage and intensity scores by pathologist
2 Based on NCCN guidelines for anti-tubulin drugs

NSCLC = non-small cell lung cancer

2024 IND
First-in-Class Potential for a 5T4-Targeted ADC with Anti-Tubulin Payload

- High affinity 5T4 monoclonal antibody conjugated to MMAE
- Site-specific conjugation:
  - Nominal Drug Antibody Ratio (DAR) = 2
- Proprietary linker technology:
  - Requires two tandem cleavage events for payload release
- Highly potent and efficacious in preclinical models

Potential for broad impact across a range of tumor types

ADC = antibody-drug conjugate
MMAE = monomethyl auristatin E
XB010 Demonstrates Superior Efficacy in Xenograft Models

Efficacy observed across a range of PDX models including breast, lung, and endometrial cancers

ADC = antibody-drug conjugate
PDX = patient derived xenograft
SEM = standard error of mean
XB628

PD-L1-NKG2A Bispecific Antibody
XB628 Simultaneously Targets Adaptive & Innate Immune Checkpoints

- High affinity PD-L1 & NKG2A binders formatted into a bispecific antibody
- Simultaneous inhibition of adaptive & innate immune checkpoints
- Acts as an NK cell engager, co-localizing NK and tumor cells
- Highly efficacious in tumor cell kill models in vitro
- B-Body® platform: high yield and efficient purification using conventional methods

**First-in-class potential for a bispecific targeting PD-L1 and NKG2A simultaneously**

*PD-L1 = programmed cell death ligand 1
NKG2A = natural killer cell receptor group 2A
NK = natural killer*
A Bispecific Targeting PD-L1 & NKG2A is a Differentiated Approach

Advantages of a bispecific over combination therapy

- Engager to co-localize/redirect NK and T cells to tumor cells for enhanced tumor killing
- Potential for improved dosing and PK/PD with bispecific compared to combination therapy

NKG2A/HLA-E

- NKG2A is an immune inhibitory checkpoint, expressed on NK cells and CD8+ tumor infiltrating lymphocytes (TILs), that binds HLA-E
- HLA-E expression is upregulated on tumor cells and acts as a potential resistance mechanism to PD-1/L1 blockade

PD-L1

- PD-L1 is overexpressed in multiple tumors
- Antibodies targeting this pathway are extensively validated, with demonstrated success in the clinic

Phase 2 COAST (JCO 2022)¹

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Treatment</th>
<th>No. of Events/Total No. of Patients (%)</th>
<th>mPFS, Months (95% CI)</th>
<th>12-month PFS Rate, % (95% CI)</th>
<th>HR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durvalumab + monalizumab</td>
<td>21/62 (33.9%)</td>
<td>15.1 (13.6 to NE)</td>
<td>72.7 (58.8 to 82.6)</td>
<td>0.42 (0.24 to 0.72)</td>
<td></td>
</tr>
<tr>
<td>Durvalumab</td>
<td>38/67 (56.7%)</td>
<td>6.3 (3.7 – 11.2)</td>
<td>33.9 (21.1 to 47.1)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Durvalumab in combination with monalizumab prolonged PFS vs. Durvalumab alone in patients with unresectable stage III non-small cell lung cancer

Simultaneous inhibition of adaptive and innate immune checkpoints with engager activity

¹ Herbst et al. JCO 2022
Synergistic MOAs + Recruitment for Direct Killing = Potential for High Impact

Engager activity co-localizes NK cells with cancer cells

Relieve inhibitory PD-L1/PD-1 checkpoint (adaptive immunity)
Relieve inhibitory HLA-E/NKG2A checkpoint (innate immunity)

Dose-Dependent Co-localization

Increased NK-Mediated Tumor Cell Killing Compared to Separate mAbs

Created with BioRender.com
XB371

Tissue Factor-TOPOi Antibody-Drug Conjugate
Building a Tissue Factor ADC Franchise: XB002 and XB371

XB002 potentially differentiates from TV on tolerability, exposure, and combinability.

XB371 is complementary, providing optionality and unlocking access to additional markets.
TF Franchise Has Broad Applicability Across Solid Tumors

Expected Payload Sensitivity for XB002 and XB371 Across Key Tumors

Anti-Tubulin Sensitive XB002

- NSCLC
- Endometrial
- Head & Neck
- Prostate

Sensitive to both XB002 and XB371

- Ovarian
- Esophageal
- Pancreatic
- Cervical
- Breast
- Bladder

TOPO Inhibitor Sensitive XB371

- SCLC
- Colorectal

Potential applicability to EXEL TF Franchise

XB002 & XB371

XB002 (TF-MTI ADC) and XB371 (TF-TOPOi ADC) are applicable across a range of solid tumors

Two distinct payload approaches provide optionality in several attractive markets
XB002 & XB371 Utilize Next-Generation Technology

XB002 & XB371 utilize a novel mAb that recognizes a TF epitope that does not interfere with Factor VII binding

- Payload uses a novel auristatin-based drug-linker that is more hydrophilic than traditional MMAE-based drug-linkers
- Potential for improved properties compared first gen, MMAE-based ADCs

FIH Study (JEWEL-101) ongoing

XB002
DAR = 3.8

XB371
DAR = 8

= MTI payload
= TOPOi payload

- Site-specific conjugation and proprietary tandem dual cleavage linker technology
- Topoisomerase inhibitor payload demonstrates potent efficacy and increased bystander effect

IND filing 2025

mAb = monoclonal antibody
TF = tissue factor
ADC = antibody-drug conjugate
MMAE = monomethyl auristatin E
FIH = first-in-human
DAR = drug antibody ratio
TOPOi = topoisomerase inhibitor
MTI = auristatin-based microtubulin inhibitor
IND = Investigational New Drug application

mAb = monoclonal antibody
TF = tissue factor
ADC = antibody-drug conjugate
MMAE = monomethyl auristatin E
FIH = first-in-human
DAR = drug antibody ratio
TOPOi = topoisomerase inhibitor
MTI = auristatin-based microtubulin inhibitor
IND = Investigational New Drug application

mta® = multi-targeted antibody
mab = monoclonal antibody
TMT = tandem dual cleavage technology
MTI = auristatin-based microtubulin inhibitor
IND = Investigational New Drug application
Potent Anti-Tumor Activity After Single XB371 Dose in Xenograft Models

**BxPC-3**
(Pancreatic Cancer)

**HPAF-II**
(Pancreatic Cancer)

**EXCELLENT TOLERABILITY IN DOSE RANGE FINDING NON-GLP TOX**
XB064

ILT2 Monoclonal Antibody
ILT2: Immune Checkpoint Potentially Associated with Resistance to Anti-PD-1

Binding of tumor cell HLA-G to ILT2 on immune cells impairs:

- Proliferation
- Cytotoxicity
- Phagocytosis
- Differentiation
- Cytokine secretion
- Chemotaxis

ILT2 = Ig-like transcript 2
PD-1 = programmed cell death protein 1
HLA-G = human leukocyte antigen G
NK = natural killer
CD8 = cluster of differentiation 8

Mandel et al., J Immunother Cancer, 2022
Hoffman et al., Front. Immunol., 2023
XB064: ILT2 Monoclonal Antibody

High affinity ILT2 mAb with best-in-class potency and activity in preclinical models

- Immune modulating checkpoint present in myeloid cells, NK cells, and T-cells
- Associated with resistance to PD-1 pathway inhibitors
- Ligand (HLA-G) highly expressed in clear cell RCC
- Opportunities to combine broadly with internal pipeline and approved IO agents

**Building IO franchise with complementary mechanisms of action**

**Definitions:**
- ILT2 = Ig-like transcript 2
- PD-1 = programmed cell death protein 1
- HLA-G = human leukocyte antigen G
- mAb = monoclonal antibody
- IO = immunotherapy
- NK = natural killer
- RCC = renal cell carcinoma
XB064 Complements Our Immuno-Oncology Portfolio

IO Pipeline

ILT2 = Ig-like transcript 2
PD-1 = programmed cell death protein 1
HLA-G/E = human leukocyte antigen G/E
mAb = monoclonal antibody
NK = natural killer
CD8 = cluster of differentiation 8
CD47 = cluster of differentiation 47
CD8-L1 = programmed cell death ligand 1
IO = immunotherapy
NKG2A = natural killer cell receptor group 2A
SIRPa = signal-regulatory protein alpha

Created with BioRender.com
XB064: Superior Activity in Functional Models Compared to Benchmarks

Higher potency and magnitude of effect with XB064 compared to clinical benchmarks

**Cytokine Release**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNγ Release</td>
<td>NK-Mediated Cytotoxicity</td>
</tr>
<tr>
<td>XB064</td>
<td>0.1</td>
</tr>
<tr>
<td>NGM707</td>
<td>0.6</td>
</tr>
<tr>
<td>BND-22</td>
<td>4</td>
</tr>
</tbody>
</table>

IC50 = half-maximal inhibitory concentration
IFNγ = interferon gamma
NK = natural killer cell

Created with BioRender.com
Small Molecule Pipeline
Small Molecules with Potential for Differentiating Clinical Activity

**XL309**
- USP1 inhibition shows synthetic lethality with BRCA1/2 mutations
- Potential superiority in safety pharmacology, toxicology, and DDIs
- Preclinical anti-tumor activity in BRCA-mutant and BRCA-wildtype

**XL495**
- PKMYT1 inhibition results in death of cancer cells with unstable genomes
- XL495 has best-in-class potential with improved selectivity and PK
- High combination potential, including with chemotherapy, PARPi and XL309

**EXEL-7871**
- PLK4 inhibition shows synthetic lethality with TRIM37 amplification
- EXEL-7871 is optimized for improved potency & selectivity with structure-based scaffold evolution

**Summary**
- USP1 = ubiquitin-specific protein 1
- PARPi = poly ADP ribose polymerase inhibitor
- DDIs = drug-drug interactions
- PKMYT1 = protein kinase membrane associated tyrosine/threonine 1
- PLK4 = polo-like kinase 4
- TRIM37 = Tripartite Motif Containing 37 gene
XL309

USP1 Inhibitor
USP1 Inhibitors: Synthetic Lethality with BRCA1/2 Mutation

USP1 is required for the Translesion Synthesis DNA Repair Pathway

USP1 inhibitor

(SSBs)

USP1

Impaired HR-mediated DNA DSB repair

Cell Death

HR-deficient tumor cell (e.g. BRCA1/2mut)

DNA replication (accumulation of DNA DSBs)

Normal cell with functional HR pathway

HR-mediated DNA DSB repair

Cell Survival

Tumor-selective cell killing

PARP inhibitor

(SSBs)

PARP

USP1 = ubiquitin-specific protein 1
PARP = poly ADP ribose polymerase
SSB = single-strand break

HR = homologous recombination

DSB = double-strand break
### Difference between XL309 and KSQ-4279 in Key Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XL309</th>
<th>KSQ-4279</th>
</tr>
</thead>
<tbody>
<tr>
<td>USP1 IC₅₀ (µM)</td>
<td>0.02</td>
<td>0.07</td>
</tr>
<tr>
<td>Cellular EC₅₀ (µM)</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>CYP Induction (&lt;10 µM)</td>
<td></td>
<td>CYP1A2 and 3A4</td>
</tr>
<tr>
<td>CYP Inhibition (&lt;10 µM)</td>
<td>CYP2C8</td>
<td>CYP2C8</td>
</tr>
<tr>
<td>Solubility @ pH 6.8 / 1.0 (mg/mL)</td>
<td>0.04</td>
<td>&gt;18 &lt; 0.001 0.005</td>
</tr>
<tr>
<td>Toxicology: exposure at MTD in rats vs efficacy exposure in mice</td>
<td>Dose-limiting tox observed at 18x (mono) and 50x (+ olaparib)</td>
<td>Dose-limiting tox observed at 6x (mono) and 13x (+ olaparib)</td>
</tr>
</tbody>
</table>

### Safety Screen Panel

<table>
<thead>
<tr>
<th>Safety Screen Panel (Ligand displacement @ 10 µM)</th>
<th>XL309</th>
<th>KSQ-4279</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine transporter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha₁A adrenergic receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha₂B adrenergic receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>µ-opioid peptide receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet-activating factor receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT₂B receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-type Ca²⁺ channel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COX2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDE4D2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**XL309 superior in safety pharmacology & toxicology, drug-like properties and DDI potential**

---

USP1 = ubiquitin-specific protein 1  
IC₅₀ = half-maximal inhibitory concentration  
EC₅₀ = half maximal effective concentration  
CYP = cytochrome p450  
MTD = maximum tolerated dose  
DDI = drug-drug interactions
XL309-USP1 Cryo-EM Structure Provides MOA Insight

Provides insight on potential resistance mechanisms and vectors for design of next-generation inhibitors
Anti-Tumor Activity with XL309 in BRCA-mt & BRCA-wt Xenografts

BRCA1-mutant Xenograft Model
(MDA-MB-436: Triple Negative Breast Cancer)

- Vehicle
- XL309 (10 mpk, BID)
- Olaparib (50 mpk, QD)
- XL309 (1 mpk, BID), olaparib (50 mpk, QD)
- XL309 (3 mpk, BID), olaparib (50 mpk, QD)

BRCA1-mutant Patient-Derived Xenograft Model
(OV0589-R7P7: Ovarian Cancer)

- Stop Dosing
- Vehicle
- XL309 (12.5 mpk, BID)
- Olaparib (50 mpk, QD)
- XL309 (12.5 mpk, BID), olaparib (50 mpk, QD)

BRCA1-wt Xenograft Model
(NCI-H1792*: NSCLC)

- Vehicle
- KSQ-4279 (60 mpk, QD)
- XL309 (30 mpk, BID)
- XL309 (100 mpk, BID)

BRCA1-wt, Patient-Derived Xenograft Model
(LD1-2032-361588†: Ovarian Cancer)

- Vehicle
- XL309 (50 mpk, BID)

*NCI-H1792 cells are BRCA1/2-wt
†LD1-2032-361588 tumor is BRCA1-wt/BRCA2-mutant

mt = mutant
wt = wild-type
NSCLC = non-small cell lung cancer

QD = daily dosing
BID = twice daily dosing

2023 IND
XL495
PKMYT1 Inhibitor
PKMYT1 Inhibition Results in Death of Cancer Cells with Unstable Genomes

PKMYT1

- PKMYT1 inhibits CDK1, preventing mitotic entry for damaged genomes
- Increased Cyclin E levels cause genome instability and DNA damage across a wide range of tumors including ovarian, endometrial, and colorectal
- Inhibition of PKMYT1 in cancer cells with high Cyclin E allows mitosis before completion of DNA synthesis, with catastrophic consequences
  - Synthetic lethality with CCNE1 amplification, or mutations in FBXW7 or PPP2R1A

Incidence

- CCNE1 amplification: 40% uterine sarcomas, 15-20% ovarian cancers, ~10% endometrial, esophageal and stomach cancers
- FBXW7 mutation: 38% uterine sarcomas, 15-20% endometrial cancers, and 15% colorectal cancers
- PPP2R1A mutation: ~8% of endometrial cancers

PKMYT1 = protein kinase membrane associated tyrosine/threonine 1
FBXW7 = F-Box And WD Repeat Domain Containing 7 gene
PPP2R1A = Protein Phosphatase 2 Scaffold Subunit A alpha gene
CDK1 = cyclin-dependent kinase 1
CCNE1 = Cyclin E1 gene
Cell Cycle Image: https://jackwestin.com/
**XL495: A Potent Inhibitor of PKMYT1 with Best-in-Class Potential**

<table>
<thead>
<tr>
<th>Potency / Parameter</th>
<th>XL495</th>
<th>RP-6306</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular TE EC$_{50}$ (nM)</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Cellular pCDK1 IC$_{80}$ (nM)</td>
<td>340</td>
<td>73</td>
</tr>
<tr>
<td>In vivo PD (pCDK1 EC$_{75}$, nM)</td>
<td>340</td>
<td>180</td>
</tr>
<tr>
<td>Kinome selectivity</td>
<td>19/374</td>
<td>30/374</td>
</tr>
<tr>
<td>Hepatocyte stability (human)</td>
<td>8% liver blood flow</td>
<td>56% liver blood flow</td>
</tr>
<tr>
<td>Predicted human t$_{1/2}$</td>
<td>17 h</td>
<td>2 h</td>
</tr>
<tr>
<td>Solubility pH 6.8 (mg/mL)</td>
<td>0.51</td>
<td>0.014</td>
</tr>
<tr>
<td>Oral bioavailability (rat)</td>
<td>76%</td>
<td>38%</td>
</tr>
</tbody>
</table>

**Kinases inhibited at 100x cellular TE EC$_{50}$**

---

**PKMYT1** = protein kinase membrane associated tyrosine/threonine 1  
**IC** = inhibitory concentration  
**EC** = effective concentration  
**PD** = pharmacodynamics  
**pCDK1** = phospho-cyclin-dependent kinase 1
XL495: Comparable or Better Efficacy vs RP-6306 In Vivo

- XL495 is predicted to have **significantly improved pharmacokinetics** in humans
- Dose projections in humans predict complete target coverage with **once-daily dosing** of XL495

**FBXW7 = F-Box And WD Repeat Domain Containing 7 gene**  
**CCNE1 = Cyclin E1 gene**  
**BID = twice daily dosing**

*RP-6306 not tolerated at 30 mpk BID*
XL495 Demonstrates High Potential for Combination Therapy

**XL495 in Combination with Carboplatin**

- XL495 single agent
- Carboplatin single agent
- XL495 + Carboplatin

**XL495 in Combination with 5-Fluorouracil**

- XL495 single agent
- 5-Fluorouracil single agent
- XL495 + 5-Fluorouracil

**XL495 in Combination with XL309 (USP1i)**

- XL495 single agent
- XL309 single agent
- XL495 + XL309

**XL495 in Combination with Olaparib**

- XL495 single agent
- Olaparib single agent
- XL495 + Olaparib

**Notes:**
- USP1i = ubiquitin-specific protein 1 inhibition
- CCNE = Cyclin E gene
- mt = mutant

**Abbreviations:**
- HCC1569
- CCNE1-amp
- MDA-MB-436
- BRCAmt

**Graphs:**
- Viability (Relative to vehicle control) vs. [Compound] (nM)

**2024 IND**

64
XL495 is Active in Combination with Gemcitabine & Irinotecan \textit{In Vivo}

**Selectivity and PK will drive differentiation of XL495 as a superior combination partner**
PLK4 Inhibitors: Synthetic Lethality with TRIM37 Amplification

PLK4

- PLK4 is a cell-cycle kinase that controls centriole duplication during S-phase
- Without centriole duplication, cell division occurs with delayed, acentrosomal spindle assembly that is highly reliant on pericentriolar material (PCM)
- TRIM37 amplification reduces PCM and inhibits acentrosomal spindle assembly, which leads to mitotic catastrophe when PLK4 is inhibited

TRIM37 is amplified in a significant proportion of neuroblastoma, breast, and lung tumors
Improved Potency & Selectivity with Structure-based Scaffold Evolution

High impact of structure-enabled design and rapid library construction

PLK4 Cellular Assay (EC$_{50}$)

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC$_{50}$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (2.35 Å)</td>
<td>&gt;20,000 nM</td>
</tr>
<tr>
<td>B (2.53 Å)</td>
<td>6090 nM</td>
</tr>
<tr>
<td>C (2.6 Å)</td>
<td>74 nM</td>
</tr>
</tbody>
</table>

PLK4 = polo-like kinase 4
EC50 = half maximal effective concentration
## EXEL Lead Compounds Demonstrate Favorable Properties for Advancement

### Potency / Parameter

<table>
<thead>
<tr>
<th></th>
<th>EXEL-7871</th>
<th>EXEL-0067</th>
<th>ORIC Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLK4 IC(_{50}) (^1), nM</td>
<td>8.3</td>
<td>3.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Aurora B IC(_{50}) (^1), nM</td>
<td>620</td>
<td>&gt; 16,000</td>
<td>380</td>
</tr>
<tr>
<td>Cellular TE EC(_{50}) (^2), nM</td>
<td>55</td>
<td>66</td>
<td>380</td>
</tr>
<tr>
<td>TRIM37 amplified viability EC(_{50}) (^3), nM</td>
<td>93</td>
<td>100</td>
<td>360</td>
</tr>
<tr>
<td>Ratio: Viability EC(<em>{50}) Non-TRIM37 amplified (^4)/ EC(</em>{50}) TRIM37 amplified</td>
<td>&gt; 54</td>
<td>38</td>
<td>5.5</td>
</tr>
</tbody>
</table>

\(^1\) Biochemical assay measuring ATP to ADP conversion, \(^2\) Cellular NanoBRET™ target engagement, \(^3\) Viability in CHP-134 cells, \(^4\) Viability in MDA-MB-231 cells

---

### Tumor Volume (mm\(^3\))

**EXEL-7871 in TRIM37-Amplified Mouse Xenograft**

(CHA134 – Neuroblastoma)

- **Vehicle**
- **ORIC Comparator (200 mpk, BID)**
- **EXEL-7871 (30 mpk, BID)**
Productive Discovery Engine Has Created a Deep IND Pipeline

**2024**
- **XB010**: 5T4-MMAE
- **XL495**: PKMYT1
- **XB628**: PD-L1-NKG2A

**2025**
- **XB371**: TF-TOPOi
- **XB064**: ILT-2
- **EXEL-7871**: PLK4

**Drug Modality**
- Orange: Small Molecule
- Blue: Bispecific Antibody
- Cyan: Monoclonal Antibody
- Pink: Antibody Drug Conjugate

**Consistent flow of development candidates targeting 2 INDs/year**

**Generating portfolio of molecules, all with potential for clinical differentiation**
Break – 10 Minutes
ZanziLintinib

Single Agent Activity, with a Favorable Tox Profile
Zanzalintinib is a Next Generation TKI that Builds on CABO’s Key Strengths, Aiming to Deliver an Improved Benefit/Risk Profile for Patients

Zanzalintinib builds on and enhances cabozantinib’s key drivers of commercial success, aiming to deliver an improved benefit/risk profile for patients

- **Cabozantinib knowledge and experience** has guided zanzalintinib development
- Retains the target kinases of cabozantinib, paired with an optimized pharmacokinetic profile, aiming to deliver **differentiated tolerability and QOL for patients, without sacrificing on strong efficacy**
- Improved benefit/risk profile has potential to position zanzalintinib as the **TKI combination partner of choice**
Zanza and cabo are potent ATP-competitive inhibitors of MET, VEGFR2, AXL and MER. Comparative testing on 430 kinases shows very similar broad profile.

- Preclinical tumor models: PK/PD and efficacy profiles reflect faster clearance of zanza.
- Altered ADME profile of zanza may translate to further differentiation of PK/PD in tumors vs normal tissue, potentially leading to improved benefit/risk profile for zanza.
Zanzalintinib (XL092) in Clear Cell Renal Cell Carcinoma: Results From STELLAR-001

Sumanta Pal, MD, FASCO
Professor, Department of Medical Oncology & Therapeutics Research
City of Hope Comprehensive Cancer Center, Duarte, CA, USA

On behalf of Jacques Medioni,1 Guillermo De Velasco,2 Jaime Merchan,3 Andrea B. Apolo,4 Yohann Loriot,5 Zhong Wang,6 Mamata Singh,6 Yijia Wang,6 Chung-Han Lee7

1APHP Hôpital Européen Georges Pompidou, Paris, France; Université Paris Cité, Paris, France; 2Hospital Universitario 12 de Octubre, Madrid, Spain;
3University of Miami Miller School of Medicine, Miami, FL, USA; 4National Cancer Institute, Bethesda, MD, USA;
5Institut de Cancérologie Gustave Roussy, Villejuif, France; 6Exelixis, Inc., Alameda, CA, USA; 7Memorial Sloan Kettering Cancer Center, New York, NY, USA*

*Affiliation where the work was conducted; current affiliation: Exelixis, Inc., Alameda, CA, USA
Zanzalintinib and Renal Cell Carcinoma

• Vascular endothelial growth factor receptor (VEGFR)-targeted tyrosine kinase inhibitors (TKIs) such as cabozantinib are a standard of care for advanced renal cell carcinoma (RCC)\(^1,2\)

• Zanzalintinib (XL092) is a novel, multi-targeted TKI that inhibits kinases including VEGFR, MET, and the TAM kinases (TYRO3, AXL, MER) with a short half-life, which may result in improved tolerability\(^3\)
  • VEGFR, MET, and the TAM kinases are involved in tumor growth, angiogenesis, and immunosuppression within the tumor microenvironment\(^4,5\)
  • Targeting MET and the TAM kinases in addition to VEGFR may prevent resistance to VEGFR inhibition\(^4,5\)

• Here, we present preliminary efficacy and safety results of single-agent zanzalintinib from the STELLAR-001 clear cell RCC expansion cohort

STELLAR-001: Key Eligibility and Endpoints in ccRCC Expansion Cohort

**Single-Agent Dose Escalation Cohorts (n=49)**
- Inoperable, locally advanced, metastatic, or recurrent solid tumor treated with zanzalintinib 10–140 mg QD

**Recommended Dose:**
Zanzalintinib 100 mg QD\(^1,a\)

**ccRCC Expansion Cohort (N=32)**
- Advanced, metastatic, or recurrent RCC with a clear cell histology (sarcomatoid features permitted)
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1
- Received 1–3 prior systemic anticancer therapies

**Safety Population N=81**
- **Primary Endpoints:** ORR and PFS rate at 6 months per RECIST v1.1 by investigator
- **Secondary Endpoint:** Safety
- **Exploratory Endpoints:** PFS and DOR per RECIST v1.1 by investigator; OS

---

1. Sharma M, et al. *Ann Oncol.* 2022;33(7_suppl):Abstract 481P. \(^a\)Treatment until lack of clinical benefit or unacceptable toxicity; treatment post-progression allowed if there was clinical benefit per the investigator.

---

ccRCC = clear cell renal cell carcinoma  
QD = once-daily dosing  
ORR = objective response rate  
PFS = progression-free survival  
DOR = duration of response  
OS = overall survival  
RECIST = Response Evaluation Criteria In Solid Tumors
## Baseline Characteristics for Patients in ccRCC Cohort

### Characteristics, n (%)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ccRCC Cohort (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>64 (39–79)</td>
</tr>
<tr>
<td>Male</td>
<td>23 (72)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>16 (50)</td>
</tr>
<tr>
<td>1</td>
<td>16 (50)</td>
</tr>
<tr>
<td>IMDC risk</td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>26 (81)</td>
</tr>
<tr>
<td>Poor</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Sarcomatoid component</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Sites of metastasis</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>12 (38)</td>
</tr>
<tr>
<td>Lung</td>
<td>20 (63)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>19 (59)</td>
</tr>
<tr>
<td>Bone</td>
<td>11 (34)</td>
</tr>
<tr>
<td>Number of metastatic sites</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (9)</td>
</tr>
<tr>
<td>2</td>
<td>8 (25)</td>
</tr>
<tr>
<td>≥3</td>
<td>21 (66)</td>
</tr>
</tbody>
</table>

### Characteristics, n (%)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ccRCC Cohort (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of prior therapy lines, median (range)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>1</td>
<td>5 (16)</td>
</tr>
<tr>
<td>2</td>
<td>14 (44)</td>
</tr>
<tr>
<td>≥3</td>
<td>13 (41)</td>
</tr>
<tr>
<td>Prior ICI</td>
<td>31 (97)</td>
</tr>
<tr>
<td>Prior VEGFR-TKI</td>
<td>26 (81)</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>17 (53)</td>
</tr>
<tr>
<td>Axitinib</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Best response to last systemic anti-cancer therapy</td>
<td>3 (9)</td>
</tr>
<tr>
<td>PR</td>
<td>16 (50)</td>
</tr>
<tr>
<td>SD</td>
<td>11 (34)</td>
</tr>
<tr>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>Prior nephrectomy</td>
<td>22 (69)</td>
</tr>
</tbody>
</table>

Data cutoff: June 10, 2023. *Total number of distinct target and nontarget sites at baseline.*
Best Response in ccRCC Cohort to Zanzalintinib

N=32

**ORR**
38% (12 PR)

**DCR\(^a\)**
88%

Data cutoff: June 10, 2023.

\(\text{aDCR is defined as proportion of patients with a best overall response of confirmed CR/PR or any single best response of SD. bCabo exposure was unknown for 1 patient.}\)

- Of the 6 patients with no prior TKI exposure, 3 were responders (50%).
- Three of the four cabo-exposed patients who responded to zanzalintinib had discontinued prior cabozantinib due to disease progression.
Best Response in ccRCC Cohort to Zanzalintinib

N=32

- ORR: 38% (12 PR)
- DCR: 88%

**Prior Cabozantinib**

- **Yes**: 24 (DCR 94%)
- **No**: 57 (DCR 86%)

**Prior VEGFR-TKI**

- **Cabo Included**: 35 (DCR 92%)
- **Cabo Excluded**: 63 (DCR 100%)

Of the 6 patients with no prior TKI exposure, 3 were responders (50%). Three of the four cabo-exposed patients who responded to zanzalintinib had discontinued prior cabozantinib due to disease progression.

**Data cutoff**: June 10, 2023.

aDCR is defined as proportion of patients with a best overall response of confirmed CR/PR or any single best response of SD.
bCabo exposure was unknown for 1 patient. cThese subgroups are not mutually exclusive.

**Abbreviations**

- ccRCC = clear cell renal cell carcinoma
- ORR = objective response rate
- DCR = disease control rate
- TKI = tyrosine kinase inhibitor
- PR = partial response
- SD = stable disease
- PD = progressive disease
- CR = complete response
- IMDC = International Metastatic RCC Database Consortium

**Legend**

- SD: Yellow
- PD: Gray
- PR: Green
Durable Responses to Zanzalintinib in ccRCC

- At a median follow-up of 8.3 months (range: 5.7–13.7), 50% of patients were continuing treatment.
- 75% of responses occurred at the first post-baseline tumor assessment, including all responders who had prior cabozantinib.
- As of Sept 6, 2023, 6 of the on-going patients have been on zanzalintinib longer than their most recent prior therapy.

Data cutoff: June 10, 2023.
Zanzalintinib Single-agent Activity in ccRCC: Case 1

- 65 year-old male, metastatic ccRCC to lung and bone 8 years following total nephrectomy
- Treatment history
  - Cabo-MK6482 (belzutifan): best response of PR; discontinued ~1 year due to toxicity
  - Nivolumab: progressed at 3 months

Started zanzalintinib 100 mg monotherapy
- Confirmed PR at 2nd post-baseline scan, bone lesions completely resolved week 25, lung lesion completely resolved week 33
- New brain lesion week 33
- No dose reductions required
Zanzalintinib Single-agent Activity in ccRCC: Case 2

• 67-year-old male with metastatic ccRCC to right adrenal gland

• Treatment history
  • 1 year of cabo-nivo: best response SD
  • 10 months of pembro + investigational agent: best response PD

Started zanzalintinib 100 mg monotherapy
• Confirmed PR at 2nd post baseline scan
• Subsequently progressed but remains on treatment beyond PD for 77 weeks
• Dose reduction to 60 mg, then 40 mg

Reduction in size of adrenal mass from baseline to week 17
## Safety Summary in 32 Patients with ccRCC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ccRCC Cohort (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure, median (range), mos</td>
<td>6.4 (1.0–13.2)</td>
</tr>
<tr>
<td>Grade 4 TEAE/TRAE, n (%)</td>
<td>1 (3) / 0</td>
</tr>
<tr>
<td>Grade 5 TEAE/TRAE, n (%)</td>
<td>3 (9) / 0</td>
</tr>
<tr>
<td>Dose modifications due to related AE, n (%)</td>
<td></td>
</tr>
<tr>
<td>Dose reduction</td>
<td>16 (50)</td>
</tr>
<tr>
<td>Dose hold</td>
<td>22 (69)</td>
</tr>
<tr>
<td>Discontinuation due to related AE, n (%)</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

Data cutoff: June 10, 2023.

**Abbreviations:**
- ccRCC = clear cell renal cell carcinoma
- TEAE = treatment-emergent adverse event
- TRAE = treatment-related adverse event
- AE = adverse event
# Zanzalintinib Single Agent Safety Compares Favorably to Cabo

<table>
<thead>
<tr>
<th></th>
<th>Zanzalintinib&lt;sup&gt;1&lt;/sup&gt; single-agent (N=32)</th>
<th>Cabozantinib&lt;sup&gt;2&lt;/sup&gt; single-agent (N=3695)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades ≥Grade 3</td>
<td>All Grades ≥Grade 3</td>
</tr>
<tr>
<td>Any</td>
<td>100% 56%</td>
<td>99.7% 82.7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>69% 3%</td>
<td>60.6% 10.9%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41% 16%</td>
<td>29.7% 13.9%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>31% 3%</td>
<td>49.7% 5.4%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>31% 0</td>
<td>9.4% 1.5%</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>25% 9%</td>
<td>&gt;10% NR</td>
</tr>
<tr>
<td>Nausea</td>
<td>25% 6%</td>
<td>45.5% 3.9%</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>22% 0</td>
<td>32.7% 4.4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19% 3%</td>
<td>31.7% 3.0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19% 0</td>
<td>53.0% 13.0%</td>
</tr>
<tr>
<td>AST increased</td>
<td>16% 0</td>
<td>21.7% 4.3%</td>
</tr>
<tr>
<td>ALT increased</td>
<td>16% 0</td>
<td>19.2% 3.6%</td>
</tr>
<tr>
<td>Palmar Plantar erythrodysesthesia (PPE)</td>
<td>9% 0</td>
<td>38.5% 9.1%</td>
</tr>
</tbody>
</table>

Low incidence of Grade 3 events and no treatment related Grade 5 adverse events for single-agent zanza

---

1. STELLAR-001 [XL092-001], 100mg ccRCC cohort mg (n=32); 2. Cabozantinib IBv19; all-grade AEs > 15%, plus PPE as AE of interest across all indications
PPE (Hand-Foot Syndrome) is a Significant Burden for Patients

- Adverse event seen commonly with early generation multi-target TKIs and chemotherapy
- Painful, debilitating swelling in palms of hands and soles of feet that is painful to touch and prone to blisters and peeling
- High-grade (interferes with activities of daily living like walking, driving, dressing) occurs in up to 17% of patients, depending on the TKI
- Mechanism is poorly understood, mainstay of treatment is dose hold

TKI = tyrosine kinase inhibitor

Zanzalintinib is Well-tolerated at **Full Dose** in Combination with ICI

<table>
<thead>
<tr>
<th></th>
<th>STELLAR-001&lt;sup&gt;1&lt;/sup&gt;</th>
<th>CheckMate 9ER&lt;sup&gt;2,7&lt;/sup&gt;</th>
<th>KEYNOTE-426&lt;sup&gt;3,5&lt;/sup&gt;</th>
<th>CLEAR&lt;sup&gt;6,3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>zanza + atezo/ave n=121</td>
<td>cabo + nivo n=323</td>
<td>axi + pembro n=432</td>
<td>len + pembro n=355</td>
</tr>
<tr>
<td>% Any Grade ≥ 3</td>
<td>60</td>
<td>75.3</td>
<td>75.8</td>
<td>82.4</td>
</tr>
</tbody>
</table>

**TKI-associated AEs Grade 3-4 %**

<table>
<thead>
<tr>
<th></th>
<th>STELLAR-001&lt;sup&gt;1&lt;/sup&gt;</th>
<th>CheckMate 9ER&lt;sup&gt;2,7&lt;/sup&gt;</th>
<th>KEYNOTE-426&lt;sup&gt;3,5&lt;/sup&gt;</th>
<th>CLEAR&lt;sup&gt;6,3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>7</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>8</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
<td>13</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>PPE</td>
<td>0</td>
<td>8</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>AST increase</td>
<td>1.7</td>
<td>3</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>ALT increase</td>
<td>2.5</td>
<td>5</td>
<td>13</td>
<td>4</td>
</tr>
</tbody>
</table>

<sup>1</sup> Zanzalintinib IB v5. Data Cutoff Feb 8, 2023. Table 26. N=121 (n=118 treated at zanza dose 80mg daily and higher)

Conclusions from ccRCC Cohort in STELLAR-001

• Single-agent zanzalintinib demonstrated promising antitumor activity in patients with heavily pretreated advanced ccRCC, with an ORR of 38% in the overall ccRCC cohort

• Antitumor activity was observed in patients who had progressed on prior VEGFR-TKIs, including cabozantinib, suggesting that zanzalintinib is able to overcome resistance to prior VEGFR inhibition
  • The ORR was 57% in cabo-naïve patients and 24% in those who received prior cabo

• Zanzalintinib appears to be generally well tolerated even in VEGFR-TKI pretreated patients
  • Patients who discontinue prior VEGFR-TKI therapy for toxicity were able to tolerate zanzalintinib
  • Rates of PPE, fatigue, diarrhea and AST/ALT elevations were relatively low compared with those reported for other VEGFR TKIs1–3
  • Full dose zanzalintinib can be combined with immune-checkpoint inhibitors, including atezolizumab, nivolumab and pembrolizumab


ccRCC = clear cell renal cell carcinoma  ORR = objective response rate  TKI = tyrosine kinase inhibitor  PPE = hand-foot syndrome  AST = aspartate aminotransferase  ALT = alanine aminotransferase
Focused Execution Drives Long-term Value Creation

Amy Peterson, M.D.
EVP, Product Development & Medical Affairs and CMO
What Disciplined Clinical Development Looks Like at Exelixis

Leverage Cabozantinib Lens for Zanzalintinib

- Build on cabozantinib clinical experience to design efficient signal verifying studies and accelerate into pivotal development
- Leverage development collaborations to derisk clinical investments

Pipeline Strategy

- Develop clinically differentiated assets that significantly improving standard of care for cancer patients
- Focus on the right strategy for the right asset: probability of success, speed to market, and value creation
- Drive right-sized growth and long-term value creation by making quick to kill decisions, taking smart risks and maximizing the life cycle of each of our assets
Differentiated Clinical Stage Programs Drive Long Term Value

**Zanzalintinib**
- Next-generation, multi-targeted TKI
- Similar kinase inhibition profile to cabozantinib, with shorter clinical half-life
- Broad applicability across multiple tumor types and novel combinations
- Encouraging data supporting broad development @ ESMO 2022, IKCS 2023

**XB002**
- Next-generation, TF-targeting ADC
- Potential differentiation across all aspects of the ADC
- Compelling early data presented at ENA 2022
- Plan to develop as monotherapy and in combinations across wide range of tumor types

**XL309**
- Highly selective, orally bioavailable small molecule inhibitor of USP1
- Best-in-class potential with broad applicability in BRCA-mutated tumors
- Strong rationale to combine with PARP inhibition
- In-licensed from Insilico Medicine in Sept. 2023
Zanzalintininib

3rd-generation VEGFR Targeting TKI
Zanzalintinib: a 3rd-generation TKI Created to Improve Risk/Benefit

Zanzalintinib Characteristics

- Potent inhibition of multiple kinases including MET, VEGFR, AXL and MER
- Optimized pharmacokinetic profile (half-life ~1 day)
- Steady state achieved more rapidly than with cabozantinib (half-life ~4 days)
- Encouraging preclinical monotherapy and combination efficacy with ICI
Zanzalintinib Development Vision: The VEGFR TKI of Choice for Monotherapy and Combinations

Expand beyond ICI-TKI success to set new standards of care with triplet / novel combinations based on disease biology and therapeutic setting

- **IO + PD-(L)1**
  - Seek opportunistic indications where TKI + ICI is not SoC and differentiate on benefit/risk profile

- **IO + PD-(L)1**
  - LAG3 | CTLA4 | TIGIT
  - Seek to differentiate TKI combos with novel IO combinations supported by zanza’s immunomodulatory activity

- **New MOAs**
  - HIF2α ± PD-(L)1 | XB002
  - Strengthen RCC leadership; develop and rapidly advance best-in-class TKI + novel MOA combinations

- **CTX**
  - Chemotherapy
  - Explore chemo combination potential to unlock additional opportunities

**Abbreviations:**
- TKI = tyrosine kinase inhibitor
- ICI = immune checkpoint inhibitor
- IO = immunotherapy
- PD-(L)1 = programmed death ligand 1 or programmed cell death protein 1
- SoC = standard of care
- LAG3 = lymphocyte-activation gene 3
- CTLA4 = Cytotoxic T-lymphocyte associated protein 4
- TIGIT = T cell immunoglobulin and ITIM domain
- MOA = mechanism of action
- HIF2α = hypoxia-inducible factor 2 alpha
- RCC = renal cell carcinoma
- CTX = chemotherapy
Zanzalintinib Phase 1/2 Studies Inform Pivotal Studies and Design

Leverage Phase 1 and 2 Studies to Support Best-in-Class Combinations, Dose Optimization, Contribution of Components, Indication Selection and Line of Entry for Pivotal Studies

**Regimens Evaluated**

**Regimens Evaluated**

**Regimens Evaluated**

**Regimens Evaluated**

**Regimens Evaluated**

**Tumor Types Explored**

**Tumor Types Explored**

**Tumor Types Explored**

**Tumor Types Explored**

RCC, UC, CRPC

RCC, UC, CRPC

RCC

NSCLC

Breast

CRC, HCC

CRC, HCC

NSCLC, SCCHN

CRC

CRC

**PD-1 = programmed death ligand 1**

**PD-1 = programmed cell death protein 1**

**LAG3 = lymphocyte-activation gene 3**

**CTLA4 = Cytotoxic T-lymphocyte associated protein 4**

**HIF2α = hypoxia-inducible factor 2 alpha**

**TIGIT = T cell immunoglobulin and ITIM domain**

**RCC = renal cell carcinoma**

**UC = urothelial carcinoma**

**CRC = colorectal cancer**

**CRPC = castration-resistant prostate cancer**

**NSCLC = non-small cell lung cancer**

**SCCHN = squamous cell carcinoma of head & neck**

**HCC = hepatocellular carcinoma**
Zanzalintinib Indication Selection Strategy Leverages Cabo Data to Inform Initial Opportunities

- What data can be leveraged to support investigating zanzalintinib in an indication?
- What patient populations have high unmet needs for better treatment options?
- What is the window of opportunity for development in the patient population?

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Cabozatinib Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabo SA</td>
<td>Cabo +ICI</td>
</tr>
<tr>
<td>GU</td>
<td></td>
</tr>
<tr>
<td>RCC</td>
<td>✓</td>
</tr>
<tr>
<td>Prostate</td>
<td>✓</td>
</tr>
<tr>
<td>Bladder</td>
<td>✓</td>
</tr>
<tr>
<td>GI</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>✓</td>
</tr>
<tr>
<td>CRC</td>
<td>✓</td>
</tr>
<tr>
<td>Gastric</td>
<td>✓</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>✓</td>
</tr>
<tr>
<td>Thoracic</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>✓</td>
</tr>
<tr>
<td>SCCHN</td>
<td>X</td>
</tr>
<tr>
<td>NSCLC</td>
<td>✓</td>
</tr>
<tr>
<td>SCLC</td>
<td>✓</td>
</tr>
<tr>
<td>GYN/Breast</td>
<td></td>
</tr>
<tr>
<td>Endometrial</td>
<td>✓</td>
</tr>
<tr>
<td>Ovarian</td>
<td>✓</td>
</tr>
<tr>
<td>HR+ BC</td>
<td>X</td>
</tr>
<tr>
<td>TNBC</td>
<td>✓</td>
</tr>
</tbody>
</table>

Zanzalintinib is uniquely positioned to leverage the breadth of experience with cabozantinib, while further advancing the standard of care with novel combinations.
Initial Pivotal Studies with Zanzalintinib Are Guided by Cabo Data and Reinforced by Emerging Data from STELLAR 001/002

**Colorectal cancer (Phase 3)**

- STELLAR 303: 3L+, non-MSI high, non-dMMR mCRC

  - 1:1 zanza + atezo
  - regorafenib

  1° Endpoint: OS in NLM population, OS in ITT

**Kidney cancer (Phase 3)**

- STELLAR 304: 1L, nccRCC: pap, unclass, translocation

  - 2:1 zanza + nivo
  - sunitinib

  1° Endpoint: PFS, ORR per RECIST v1.1

**Head and Neck cancer (Ph2/3)**

- STELLAR 305: PD-L1+ 1L metastatic SCCHN

  - 1:1 zanza + pembrolizumab

  1° Endpoint: PFS, OS

**Supportive STELLAR Data**

- STELLAR-001: zanza vs zanza + atezo in 2/3L mCRC
- STELLAR-002: zanza + nivo in ≥2L mCRC

**Initial Cabo Guiding Data**

- Cabo + ICI² 3L+ mCRC, N=29
  - 28% ORR

**Initial Pivotal Studies**

- Cabo + ICI² 1L/2L nccRCC, N=40
  - ORR: 54% 1L, 36% 2L

- Cabo + ICI² 1L SCCHN, N=36
  - 52% ORR

---

1L = first-line
2L = second-line
3L = third-line
NLM = non-liver metastasis
OS = overall survival
ITT = intent to treat population
MSI = microsatellite instability
mCRC = metastatic colorectal cancer
dMMR = deficient mismatch repair
ICI = immune checkpoint inhibitor
ORR = objective response rate
nccRCC = non-clear cell renal cell carcinoma
SCCHN = squamous cell carcinoma of head & neck
PD-L1 = programmed death ligand 1
RECIST = Response Evaluation Criteria in Solid Tumors
unclass = unclassified
PS = progression-free survival
OS = overall survival

1. Saeed A et al. ASCO GI 2022 Abs 135,
2. Lee CH, et al. ASCO 2023 Poster Abs 4537
# Zanzalintinib Current Clinical Development Program is Robust

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Combination(s)</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STELLAR 303</strong></td>
<td>Advanced/Metastatic Microsatellite Stable (MSS) Colorectal Cancer (CRC)¹</td>
<td>zanzalintinib + atezolizumab (vs. regorafenib)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STELLAR 304</strong></td>
<td>Advanced Non-clear Cell Renal Cell Carcinoma (nccRCC)²</td>
<td>zanzalintinib + nivolumab (vs. sunitinib)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STELLAR 305</strong></td>
<td>Squamous Cell Carcinoma of the Head &amp; Neck (SCCHN)³</td>
<td>zanzalintinib + pembrolizumab (vs. pembrolizumab)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STELLAR 001</strong></td>
<td>Multiple Solid Tumors⁴</td>
<td>zanzalintinib + atezolizumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STELLAR 002</strong></td>
<td>Multiple Solid Tumors⁵</td>
<td>zanzalintinib + nivolumab +/- ipilimumab (CTLA-4) or relatlimab (LAG-3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STELLAR 009</strong></td>
<td>Advanced Clear Cell Renal Cell Carcinoma (ccRCC)⁶</td>
<td>zanzalintinib + AB521 (HIF2α) +/- PD-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MORPHEUS LUNG</strong></td>
<td>PD-L1+ Non Small Cell Lung Cancer (NSCLC)⁷</td>
<td>zanzalintinib + atezolizumab + tiragolumab (TIGIT)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**PD-L1** = programmed death ligand 1  
**PD-1** = programmed cell death protein 1  
**LAG3** = lymphocyte-activation gene 3  
**CTLA4** = Cytotoxic T-lymphocyte associated protein 4  
**HIF2α** = hypoxia-inducible factor 2 alpha  
**TIGIT** = T cell immunoglobulin and ITIM domain
XB002

Next-generation TF-targeting ADC
XB002 (Next-generation TF-targeting ADC) Indication Selection Strategy Leverages Non-Clinical and Clinical Data

Rational selection of potential indications further profiled on unmet need, probability of success, speed to market and value proposition

- What tumor types express TF?
- Which of those are responsive to tubulin inhibitors?
- What Tivdak data can be leveraged to assess best-in-class potential of XB002?
High Intact ADC Exposure and Low Free Payload with XB002

Intact ADC

Free Payload

2 mg/kg of XB002 compared to 2 mg/kg Tivdak:

- **2x higher** Intact XB002 ADC exposure compared to Tivdak ADC
- **10x lower** Circulating MTI payload exposure compared to Tivdak MMAE payload

ADC = antibody-drug conjugate  
LLOQ = lowest limit of quantitation  
Conc = concentration  
MTI = auristatin-based microtubulin inhibitor  
MMAE = monomethyl auristatin E  
Data cut date: 4/5/23
Substantial Development Potential for XB002 as Monotherapy or in Combination

**Combine with IO to Improve Patient Outcomes**

**Maximize XB002 Development Opportunities**

**Internal Combinations Increase Portfolio Value**

<table>
<thead>
<tr>
<th>XB002 + PD-(L)1</th>
<th>XB002 Monotherapy</th>
<th>XB002 + Zanzalintinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Small Cell Lung Head &amp; Neck</td>
<td>mCRPC</td>
<td>Non-Small Cell Lung Head &amp; Neck</td>
</tr>
<tr>
<td>Esophageal</td>
<td>Esophageal, Pancreatic</td>
<td>Endometrial Ovarian</td>
</tr>
<tr>
<td>Cervical Breast</td>
<td>Non-Small Cell Lung Head &amp; Neck</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endometrial, Cervical, Ovarian, Breast</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TF+ Solid Tumors</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations**

- IO = immunotherapy
- PD-L1 = programmed death-ligand 1
- mCRPC = metastatic castration-resistant prostate cancer
- TF = tissue factor
- GU = genitourinary tumors
- GI = gastrointestinal tumors
- GYN = gynecologic tumors
XL309

A small molecule inhibitor of USP1
XL309 Has Potential to Deepen and Prolong Responses to PARPi and May Provide Benefit to a Broader Population

Maximize Life-cycle Management Potential

Accelerate Development

Platinum Sensitive

HRD-ness

BRCAmnt

PARPi Refractory

XL309 + TBD (platinum-based chemo, maintenance post platinum)

XL309 + PARPi

XL309 + XL495/TBD

XL309 Monotherapy

XL309 + PARPi ± XL495

XL309 Monotherapy

XL309 + XL495

PARPi = poly ADP ribose polymerase inhibitor
HRD = homologous recombination deficiency
BRCAmnt = BRCA mutation positive
Cabozantinib

Life-cycle Management/Value Creation
Three Positive Phase 3 Data Readouts for Cabozantinib in Third Quarter 2023

**CONTACT-02**

1L/2L mCRPC

**Key Endpoints**
- **Primary:** BICR-PFS, OS
- **Secondary:** BIRC-ORR, DOR, PSA

**CONTACT-02:** Pivotal phase 3 study of cabozantinib + atezolizumab vs. 2nd NHT in patients with previously treated mCRPC
- Top-line press release announcing positive PFS results on August 21st
- Data presentation targeted for early 2024

**CABINET**

2L pNET and epNET

**Key Endpoints**
- **Primary:** BICR-PFS
- **Secondary:** OS, ORR, Safety

**CABINET:** Two pivotal phase 3 studies conducted by The Alliance for Clinical Trials in Oncology evaluating cabozantinib vs. placebo in patients with either advanced pancreatic (p) or extra-pancreatic (ep) neuroendocrine tumors (NET)
- Top-line press release announcing positive results on August 24th
- Data presented by Dr. Jennifer Chan at 2023 ESMO Congress on October 22nd

---

1L = first-line
2L = second-line
PFS = progression-free survival
OS = overall survival
ORR = objective response rate
DOR = duration of response
PSA = prostate-specific antigen
NHT = novel hormonal therapy
pNET = pancreatic neuroendocrine tumors
epNET = extra-pancreatic neuroendocrine tumors
mCRPC = metastatic castration-resistant prostate cancer
BICR = blinded independent central radiology review
ESMO = European Society for Medical Oncology
Cabozantinib Extends Progression Free Survival by >3x in pNET and by >2x in epNET vs Placebo

**Pancreatic (p) NET**

- Stratified HR = 0.27
  (95% CI: 0.14 – 0.49)
  log-rank p<0.0001

- Median PFS:
  Cabozantinib = 11.4 months
  Placebo = 3.0 months

**Extra-pancreatic (ep) NET**

- Stratified HR = 0.45
  (95% CI: 0.31 – 0.66)
  log-rank p<0.0001

- Median PFS:
  Cabozantinib = 8.3 months
  Placebo = 3.2 months

---

pNET = pancreatic neuroendocrine tumors
epNET = extra-pancreatic neuroendocrine tumors
HR = hazard ratio
CI = confidence interval
PFS = progression-free survival
Vision for Development Will Bring Value to Patients

**Biology-centric**
- Validated/known targets
- Characterize differentiation for best-in-class opportunity
- Rational combinations/indications

**Efficient**
- Leverage existing data
- Speed to monotherapy and combination dose
- Rapidly accelerate to pivotal trials

**Experienced**
- Scale appropriately
- Decide with discipline
- Build upon strong relationships

**Combinations/Approaches**
- Leverage internal pipeline and external collaborations
- High probability of success programs
- Best-in-class/first-in-class potential

**Industry-Leading Cycle Times**
- Data-driven decision-making
- Streamline operations to enhance speed of clinical execution
- Quick to kill and quick to go decisions

**Partner of choice**
- Patient and investigator focused
- Partner with companies that are aligned with our strategic interests
- Collaborate for optimal outcomes
Closing Remarks

Michael M. Morrissey, Ph.D.
President and CEO
## Exelixis R&D: Uniquely Positioned to Drive Value Creation

| Value Creation | 2023 | 2024-2027 | 2028+
|----------------|------|-----------|------
| Maximize cabo LCM to fuel clinical pipeline expansion | | | |
| Focus on mCRPC.NET and continued commercial execution in RCC/HCC/DTC | | | |
| Expand beyond cabo with zanza, XB002, XL309 | | | |
| Potential for first pivotal read-outs from zanza and XB002 in core commercial indications | | | |
| Multiple product launches with broad patient impact across solid tumors | | | |
| Balanced portfolio of clinically differentiated assets across small molecules and biotherapeutics | | | |

**Abbreviations:**
- **LCM** = life-cycle management
- **mCRPC** = metastatic castration-resistant prostate cancer
- **NET** = neuroendocrine tumors
- **RCC** = renal cell carcinoma
- **HCC** = hepatocellular carcinoma
- **DTC** = differentiated thyroid cancer

**Acronyms:**
- **cabo** = cabozantinib
- **zanza** = zan股本
Break – 10 Minutes
Q&A Session

Exelixis R&D Day: Science & Strategy
Thank You

Exelixis R&D Day: Science & Strategy