Glycyx

Eliminating barriers to immunotherapy efficacy

Glycyx Therapeutics

January 2025

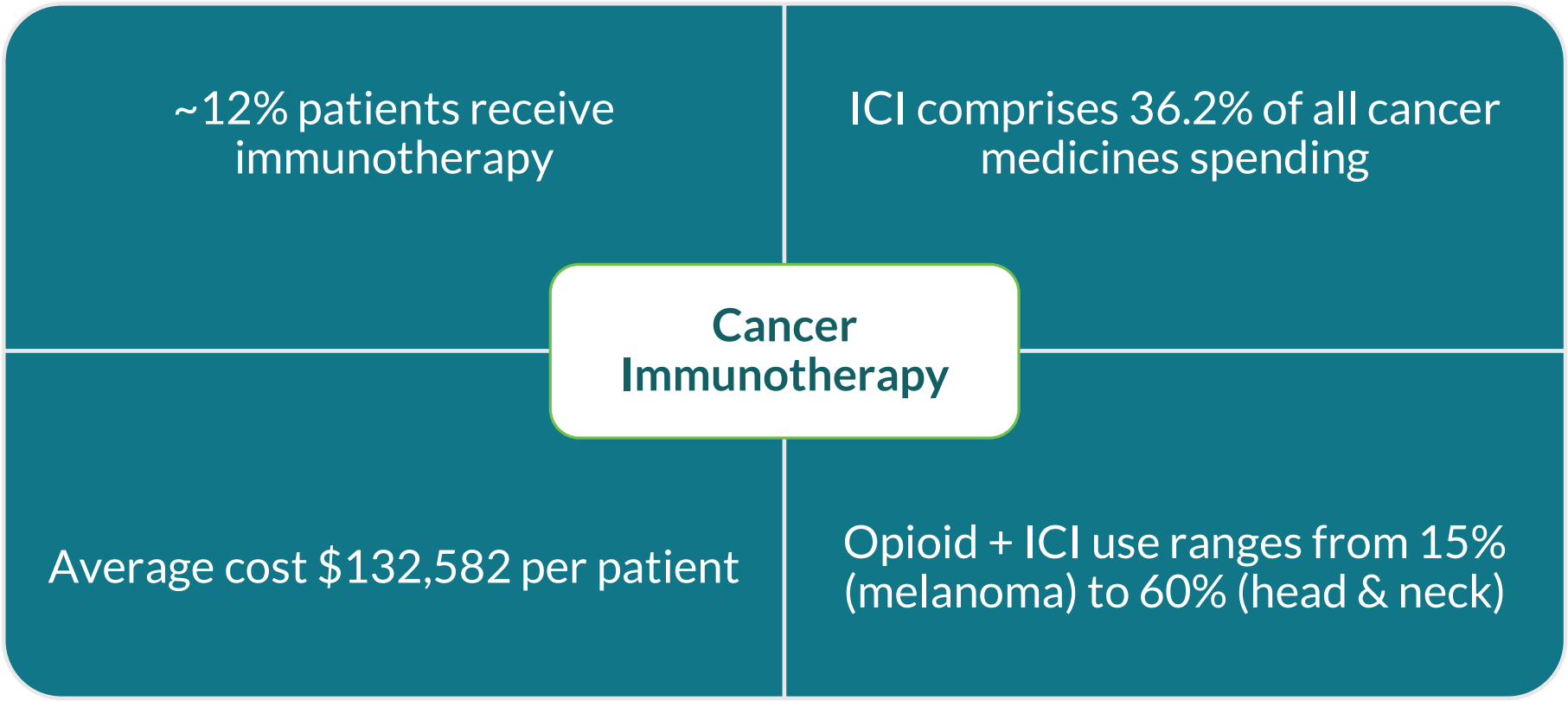
Mission

Preventing immunodeficiency in cancer caused by opioids used for pain management

Opioids are essential for cancer pain but they block immunotherapy

Glycyx is creating a new standard of care to ensure optimal outcome and pain relief for every patient

45% of immunotherapy patients take opioids for pain, and there are no good alternatives

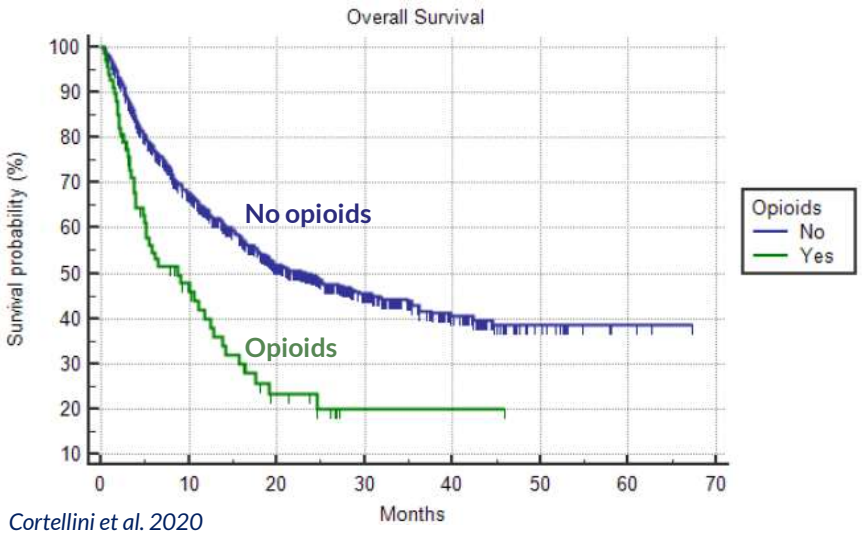


ICI, immune checkpoint inhibitor(s)

Opioids block efficacy of checkpoint inhibitors

Opioid-Induced Immunodeficiency (OII) in frontline checkpoint inhibitor patients

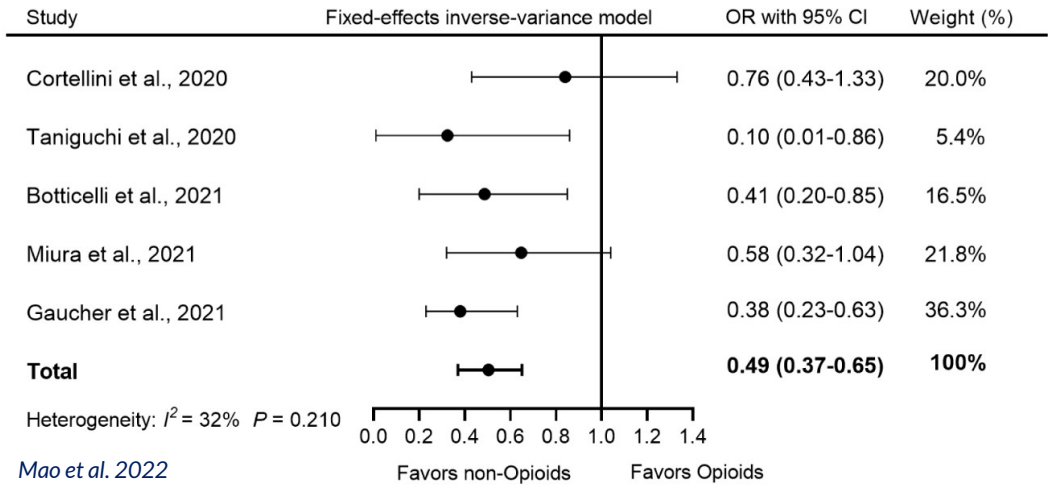
Opioids Are First Line For Cancer Pain



Cortellini et al. 2020

Patients on ICI survive significantly longer without opioids…

Opioids Create Immune Deserts in TME



Mao et al. 2022

…and this evidence is across 4000 patients

Real world observational evidence:

- Baseline opioid status associated with poor survival of immunotherapy patients in multiple observational studies
- Cortellini et al. results at left confirmed in **propensity score matching analysis**
- Published meta-analysis shows **HR for OS = 1.78; HR for ORR = 0.49**

TME, Tumor microenvironment

Our lead, axelopran, is clinic-ready in 2024

Within striking distance of key milestones to start a Phase 2a POC study

Safety

- Axelopran is a small molecule, **peripherally active mu receptor antagonist** that competitively binds on T-cells, in the body outside the CNS, and in the tumor microenvironment
- Axelopran is a safe, **immune restoration and maintenance** agent preventing Opioid-Induced Immunodeficiency by preparing the immune system prior to immunotherapy
- Bioavailable, efficacious dose regimen demonstrated in OIC Phase 2: **15mg** oral daily
- Extensive safety database: **544 patients dosed**; minor and transient side effects; no treatment discontinuation and **no Grade 3+ AEs**

Regulatory

- **IND #078-654** opened with GI division of FDA by Theravance; transferred to Glycyx
- **IND reactivated** with GI division **Apr 5, 2024**; transfer to (or new IND submission to) Oncology Division Q1 2025

Manufacturing

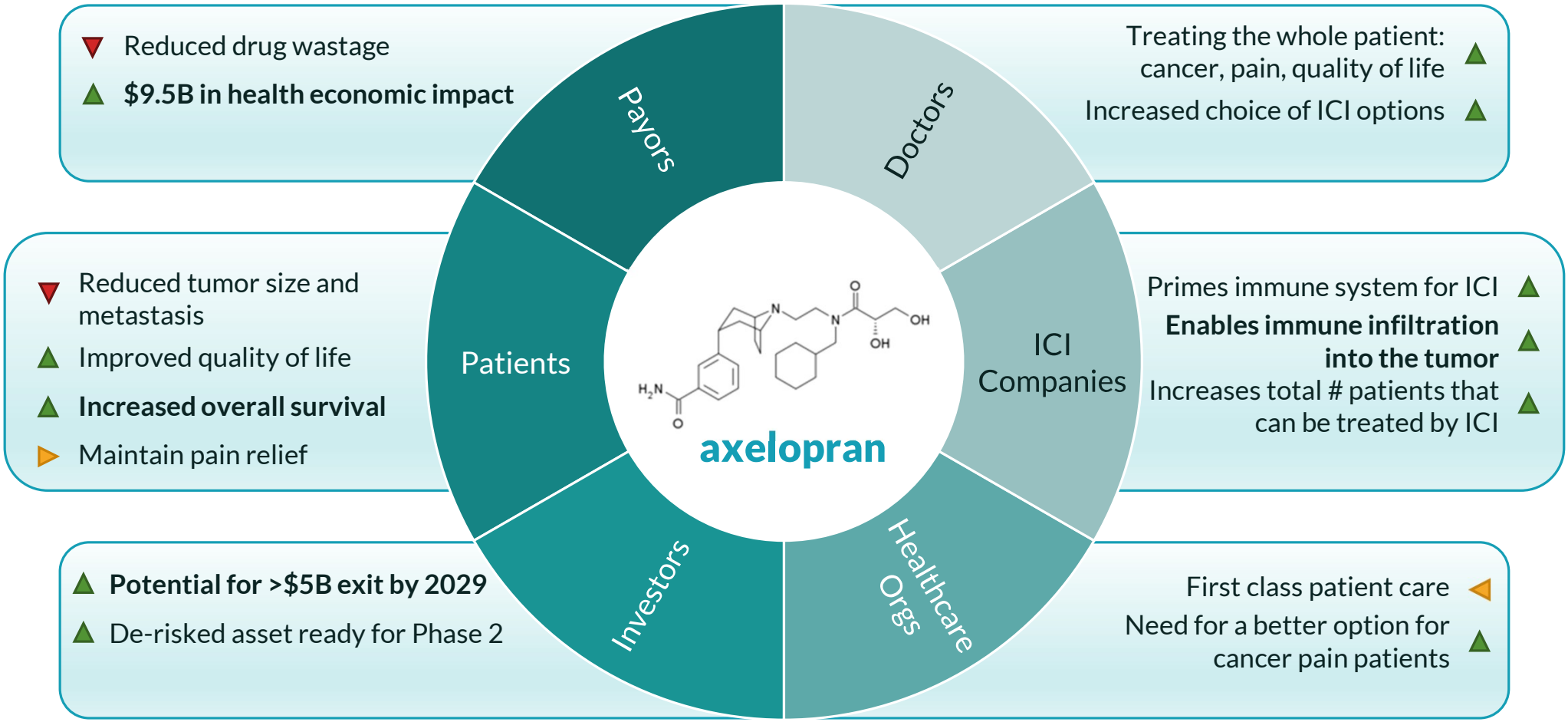
- CMC validated to 12kg batches; long-term manufacturing partnership
- **11kg** batch produced by Scinopharm Taiwan in Q1 2024 = **~2,000 patient years of API**

Clinical Partners

UPMC LIFE CHANGING MEDICINE
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History
SAPIENZA UNIVERSITÀ DI ROMA
Mass General Brigham
Dana-Farber Cancer Institute
Memorial Sloan Kettering Cancer Center
MAYO CLINIC
HealthPartners Park Nicollet
JOHNS HOPKINS MEDICINE
EMORY UNIVERSITY SCHOOL OF MEDICINE

Axelopran

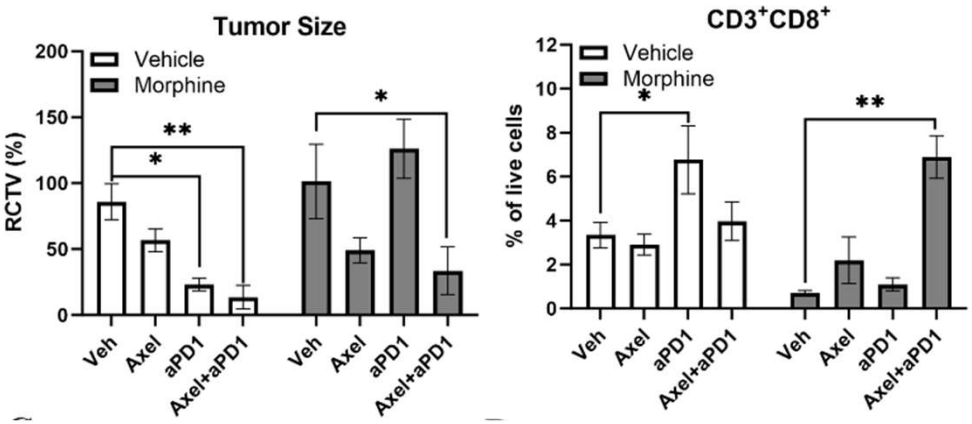
An immune restoration and maintenance agent for better patient outcomes



Proof of Mechanism

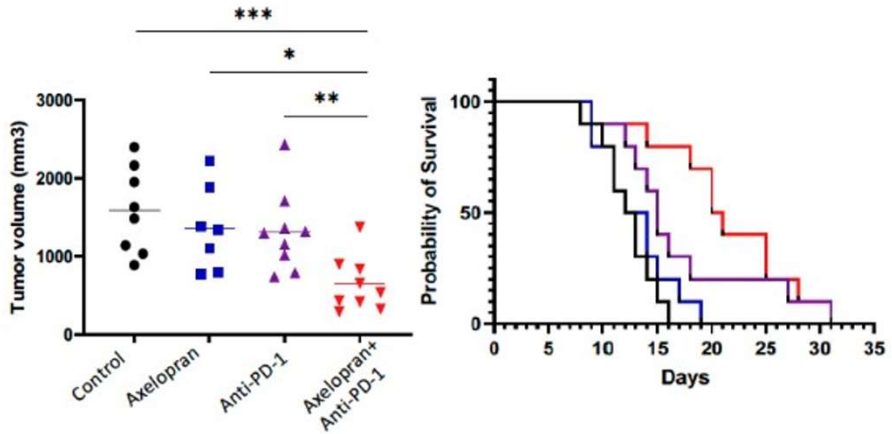
Axelopran prevents Opioid-Induced Immunodeficiency, maximizing ICI efficacy

Axelopran improves tumor burden in opioid-induced immunodeficiency in murine syngeneic oral cancer (HNSCC)



Scheff and Johnson, 2024 (publ. submitted)

Axelopran improves survival even absent prescription opioids in murine syngeneic colon cancer (CRC)



Axelopran improves immune profile and survival in models replicating clinical observations with opioids/ICI:

- **Reverses opioid suppression** of CD8+ T-cell infiltration
- **Improves biomarkers of tumor microenvironment** such as TIM3 and PD-1
- **Reduces tumor burden** in multiple solid tumor models (HNSCC, CRC, Melanoma, TNBC)
- **Mono- and combo-therapy approaches** independent of prescription opioids, providing expansion opportunities

US Market Opportunity

Glycyx

IMMUNOTHERAPY MARKET: OPDIVO + KEYTRUDA

Despite biosimilars, PD-1's and immunotherapies expected to grow through 2030

$32B

CANCER PAIN MARKET: OPIOIDS

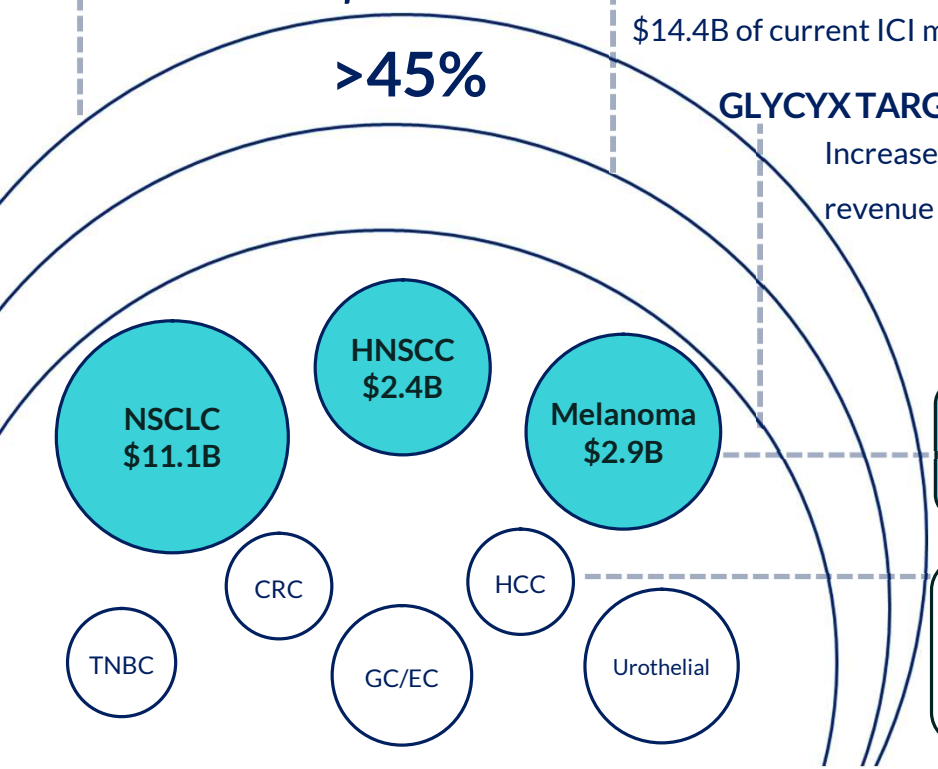
45% of immunotherapy patients take opioids

$14.4B of current ICI market is wasted spend

>45%

GLYCYX TARGET MARKET: OPIOID + ICI

Increase responsiveness of ICIs and revenue of axelopran >$1B



First 3 basket indications with >$15B PD-1 market

Follow-on indications maximize long-term immunotherapy market capture

Axelopran is an immune restoration agent for all ICIs in solid tumors

- Enables tumor infiltration
- Study designed for broad label in solid tumor enhancer of ICIs with opioids

Indication	Anti PD-1 Market ($M)	Opioid Use	Peak Penetration
HNSCC	$2,443	70%	50%
NSCLC	$11,144	45%	30%
Melanoma*	$2,861**	15%	50%

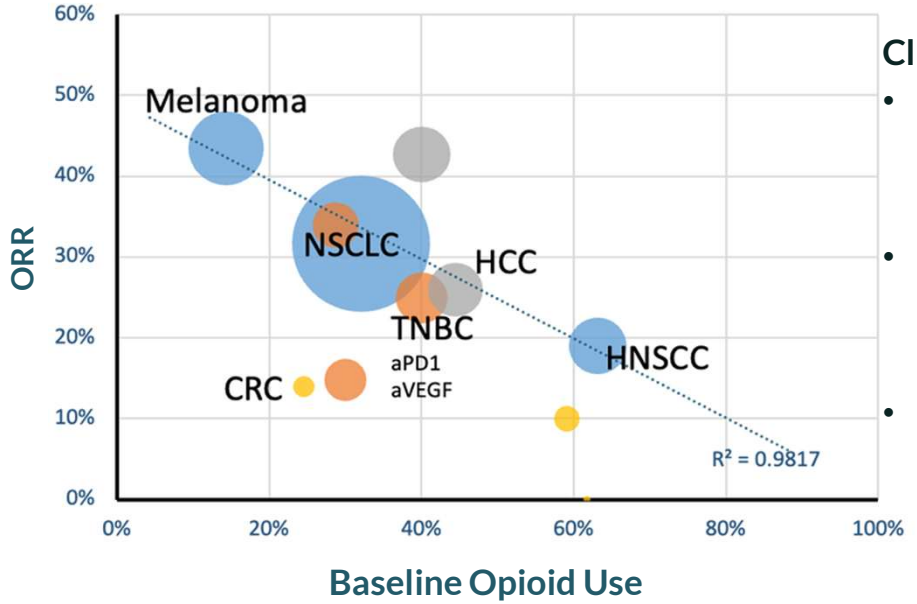
** Highest producer of endogenous opioids*
***Does not include approved LAG3 and CTLA4 immunotherapy combo agents*

Pipeline:

Ready to start a full Phase 2b POC study with full funding

Therapy	Tumor Type	Phase 1	Phase 2	Phase 3	Est. Launch	Comments
ICI Monotherapy + Axelopran	HNSCC				2030	Basket Phase 2a study in three indications. Open-label, Simon 2-stage design de-risks Phase 2b expansion
	NSCLC					
	Melanoma					
ICI Combination + Axelopran	Solid tumors				2032	Follow on indications for label expansion: GC/EC, Urothelial, CRC, TNBC, HCC

Rationale



Clinical Plan:

- HNSCC is the ideal indication for a proof-of-concept: 70% opioid use + 85% immunotherapy eligibility **provides fast enrollment of eligible patients**
- NSCLC and Melanoma included due to significant market size enhanced by concomitant opioid use *(see graph, left)*
- **Simon 2-stage trial design gives insight to efficacy and powering for a de-risked Phase 2b**, by using a smaller, less expensive open-label design

Go to market strategy:

Strategic development plan consistent with successful precedents

Business Development opportunities following proof of concept data

	De-risking next-gen pipelines	Oral immunotherapy combinations	Supportive care in oncology
MERCK	X	X	
Bristol Myers Squibb	X		
Roche	X		
HELSINN			X
CURIS		X	
AMGEN	X	X	
Incyte		X	

Axelopran holds patent protection for fixed-dose combination therapies, with conversations initiated for oral PD-1 combinations.

Expansion to other immunotherapies unlocks new opportunities for growth and partnership.

Comparable asset: Karuna's development of an agonist/antagonist combination

KarXT *(xanomeline-trospium combination therapy)*

2012	Karuna licenses de-risked asset from Eli Lilly with hundreds of patients-worth of safety data
2012-2018	KarXT incubation within PureTech Health
	Glycyx at present
2018-2019	Raises $42M Series A and $80M Series B
2019	$103M IPO and successful Phase 2 in first indication
2022	Positive Phase 3 readout in first indication
2023	$14B acquisition by BMS

Major similarities and takeaways

Successful repurposing with combination approach	Karuna **enhanced agonist efficacy while reducing antagonist AEs**; axelopran+ICI aims for similar results, boosting efficacy while preserving opioid analgesia.
Accelerated development	Licensed a de-risked asset **leverages a robust safety database**, shortening clinical development timelines.
Multi-indication potential following PoC in lead indication	Karuna's success in schizophrenia as rational first neuro indication **informs Glycyx's strategy for HNSCC** (high opioid+ICI combination).

Development Plan

Simon 2-stage design: Basket Phase 2b study of 3 cancers with a registrational intent

1st-stage:

Safety / futility with initial efficacy readout

$15M

HNSCC
N = 18

6 month recruitment
ORR 8 weeks

With standard of care ICI and opioid

NSCLC
N =18

6 month recruitment
ORR 8 weeks

With standard of care ICI and opioid

Melanoma
N = 18

6 month recruitment
ORR 8 weeks

With standard of care ICI and opioid

Raise $5M to focus on melanoma study to answer request from VCs on POC efficacy

Adaptive design to determine final patients number required for registration

2nd-stage:

Efficacy with registration intent

$50M - $80M

HNSCC
N = 120 to 200

Randomized controlled standard of care ICIs and opioid

With and with out axelopran

NSCLC
N = 120 to 200

Randomized controlled standard of care ICIs and opioid

With and with out axelopran

Melanoma
N = 120 to 200

Randomized controlled standard of care ICIs and opioid

With and with out axelopran

Designed for broad label for solid tumors outside the brain

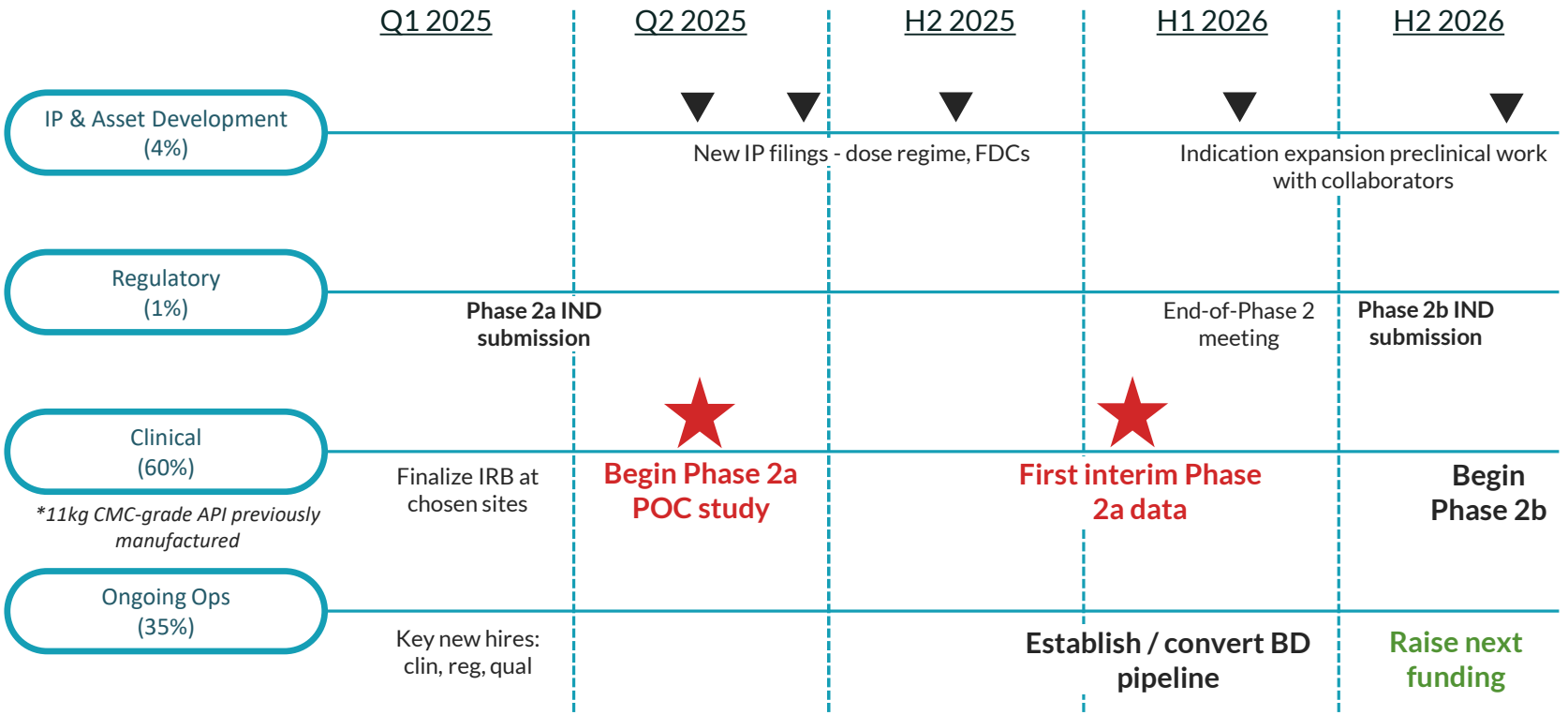
Ask and Use of Proceeds

Raising $5M Series A for a POC in human in melanoma

Glycyx

2yr Key Milestones

- Begin Phase 2 – Simon 2 stage
- Complete Part 1 of Phase 2 study
- Convert pipeline of partnerships



Accomplishments and Funding Positioning

Oncology efficacy potential fully established, ready for full Phase 2b/3 RCTs.

Established pipeline partnerships on late-stage portfolio asset.

Situate for larger round with large VCs

Potential for IPO or acquisition in 2 to 3 years

Expected to be >$2B exit, treating 50,000 to 100,000 patients

Glycyx

TAM – Solid Tumors with anti-PD1s and Opioids

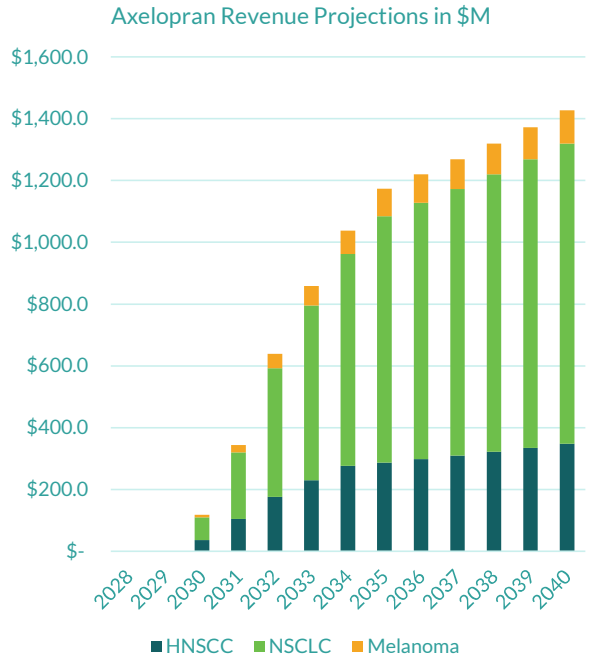
Opioid-Induced Immunodeficiency

- Opioids used in 45% of cancer immunotherapy patients
- Opioids block checkpoint inhibitors (ICI) through immunosuppression
- Potential to increase overall survival by 50% across all solid tumors where opioids and ICIs are used

Patients

- 50,000 eligible patients in 3 cancers alone, potential up to 100,000
- Better quality of life while still maintaining pain relief and survival

Revenue projections on HNSCC, NSCLC and Melanoma



Investor Returns

Series Seed - $5M

- Clean cap table
- Only internal investors for valuation designed for de-risked step-up
- Clear milestones and deliverables on Phase 2 study

Team

Glycyx

Scientific, clinical & commercial experts in cancer and opioid biology.

Lorin K. Johnson, PhD
Chairman & CSO
Scientific founder of Salix,
13 NDAs in GI Medicine
$15B exit

Justin Chickles, MBA
Chief Executive Officer
CEO, CCO, CPO roles
25+ years leadership experience:
start-ups, J&J, other pharma

Dave Taggart, LLM
Chief Business Officer
R&D, BD, and strategic
consulting at AbbVie, J&J,
BMS, Sanofi, Roche

Bridget Martell, MD
Chief Medical Officer
C-suite roles at Artizan Bio, Kura
Oncology, Juniper Pharma
Led 6 medicine approvals
including Kadcyla & Elelyso

Prof. Jonathan Moss, MD, PhD
Chief Medical Advisor
University of Chicago
Anesthesiologist & inventor of
the PAMORA class of drugs

Key Advisors

Ana Anderson, PhD
Harvard Medical School
Associate Professor, Center
for Neurological Diseases

Dylan Zylla, MD
HealthPartners
Medical Oncologist

Alessio Cortellini, MD
University of Roma
Medical Oncologist

Dan Zandberg, MD
UPMC
Associate Professor
Medical Oncologist

Nicole Scheff, PhD
UPMC
Assistant Professor
Center for Neuroscience

Join us in eliminating barriers to immunotherapy efficacy

Glycyx

- Cancer is a complex, multi-factor disease
  - We have identified a clear problem with current treatments
  - And there is no reason for patients not to treat both the pain and the cancer
  - Axelopran can significantly improve survival and still maintain pain relief
- We want a partner that can join us on the journey on bringing this important treatment to market

Contact Us

Justin Chickles, CEO

justin@glycyxtherapeutics.com

+1 203-914-5375

www.glycyxtherapeutics.com

Appendix

Glycyx Solution

Axelopran is a best-in-class opioid receptor antagonist demonstrating improved cancer survival while maintaining the analgesic effects of cancer pain medication

Selective and potent: Peripherally active mu-opioid receptor antagonist (PAMORA) mechanism retains opioid pain relief in cancer patients while eliminating immunosuppressive effects.

Proven safety, tolerability, & CMC: Axelopran previously studied in >500 patients across nine trials in OIC, with no significant AEs. Full preclinical toxicology program and CMC package complete with 11kg API available.

Best-in-class and first-in-indication: Three PAMORAs are approved for OIC but not cancer indications, including combination therapy with checkpoint inhibitors.

Wholly owned compound with new IP: Glycyx completed a full license for all territories and indications from Theravance before developing intellectual property with protection to 2042.

IND approved to treat cancer patients with clear path to market: Pivot to cancer indications provides FDA-aligned roadmap for development and first approval by 2030.

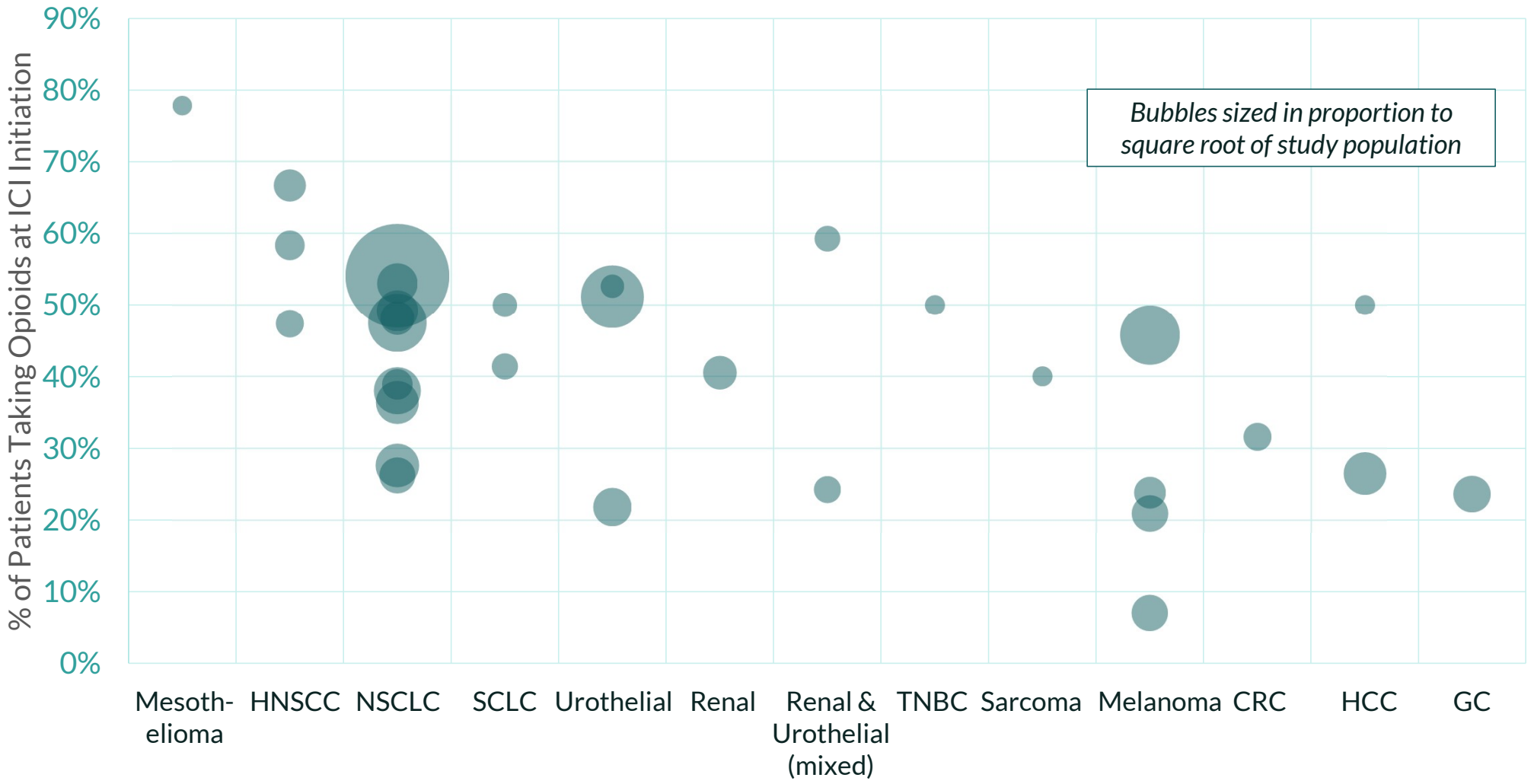
OIC, Opioid-induced constipation

Risk analysis and mitigation:

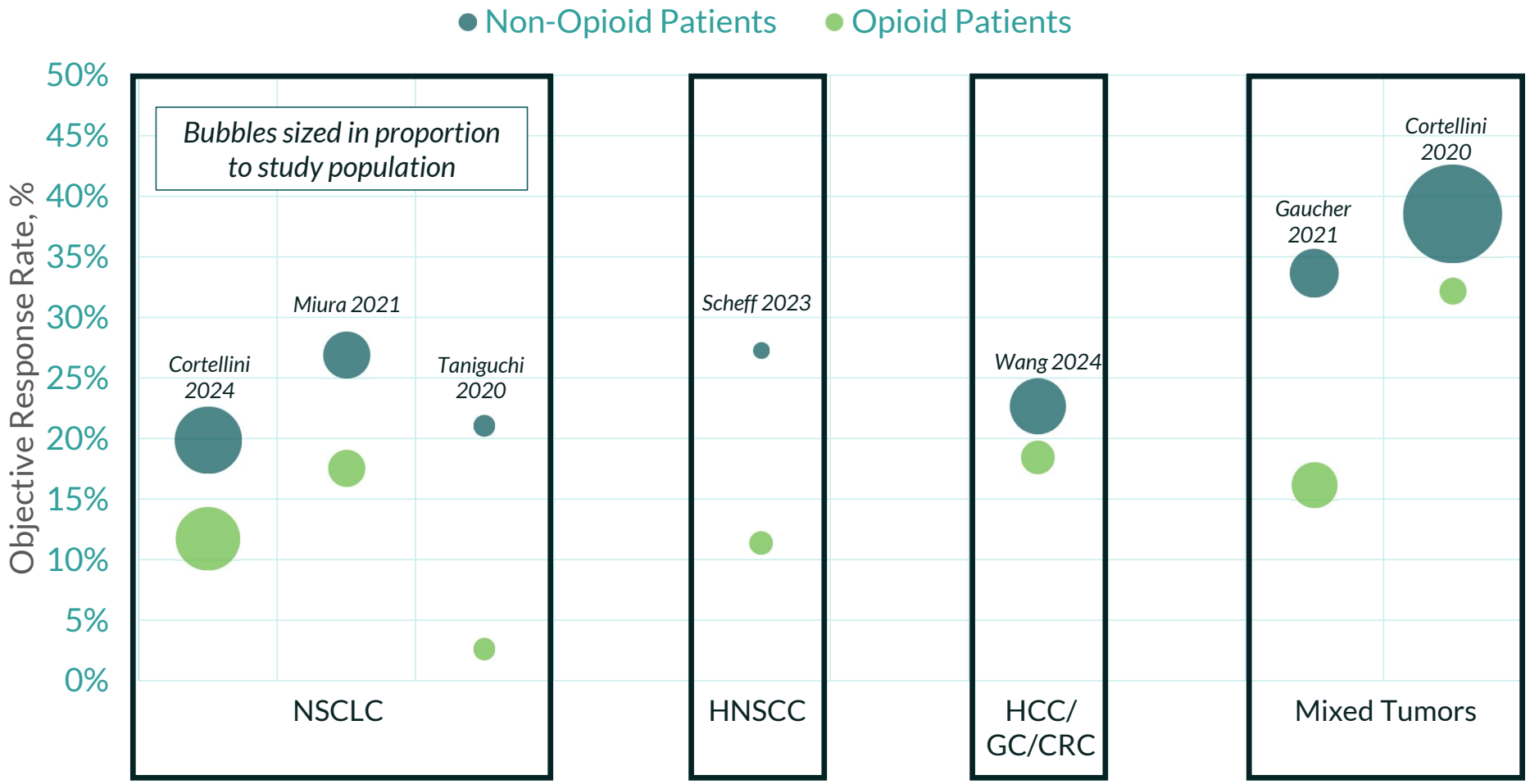
Proactively addressing potential obstacles and questions in development and marketing

Risks and Questions	Impact and Mitigation
Is there patent protection beyond 2027 for Axelopran?	• **Yes:** Glycyx retains invention and exclusivity for **Method of Use out to 2042** (combo with checkpoint and VEGF inhibitors, preventing opioid-induced immunodeficiency) in all planned indications • **Orange Book eligible:** all prosecuted patents are eligible for protection via Paragraph 4 (generics) • **Orphan Drug Designation** fortifies IP position in certain niche cancers
What happens to the target market when Keytruda and Opdivo go off-patent in 2030?	• **Limited impact:** 11 PD-1 biosimilars poised to launch as replacement, with branded PD-1 usage estimated to decline only -3% from peak by end of decade • **87% of total cancer pain market** is estimated to utilize mu opioid receptor agonists – the target of axelopran – up from 70% in 2023
Are opioids prescribed only for cancer patients with advanced disease?	• **No:** Opioids are **prescribed at all stages of cancer progression**, not just advanced stages • Glycyx mechanistically proved that opioids reduce efficacy of immunotherapies *in vivo*, and that axelopran reverses this effect • Academic collaborators have shown **opioid effect is independent of cancer stage**
Will competition from generic PAMORAs reduce profitability?	• **Unlikely:** No PAMORA has been used in for oncology combination therapy, providing **Glycyx a first-mover advantage in oncology** • **Projected >$1B in sales with focus on volume:** A broad, multi-indication label as an enhancer for immunotherapy, delivered as frequently as opioids with competitive pricing to LAG3 or CTLA4 agents
Why was Axelopran's development discontinued by Theravance?	• **Business decision in separate indications:** Theravance discontinued axelopran for business reasons after pursuing only opioid-induced constipation • Theravance has no interest in oncology evidenced by the **buyout option available to Glycyx**

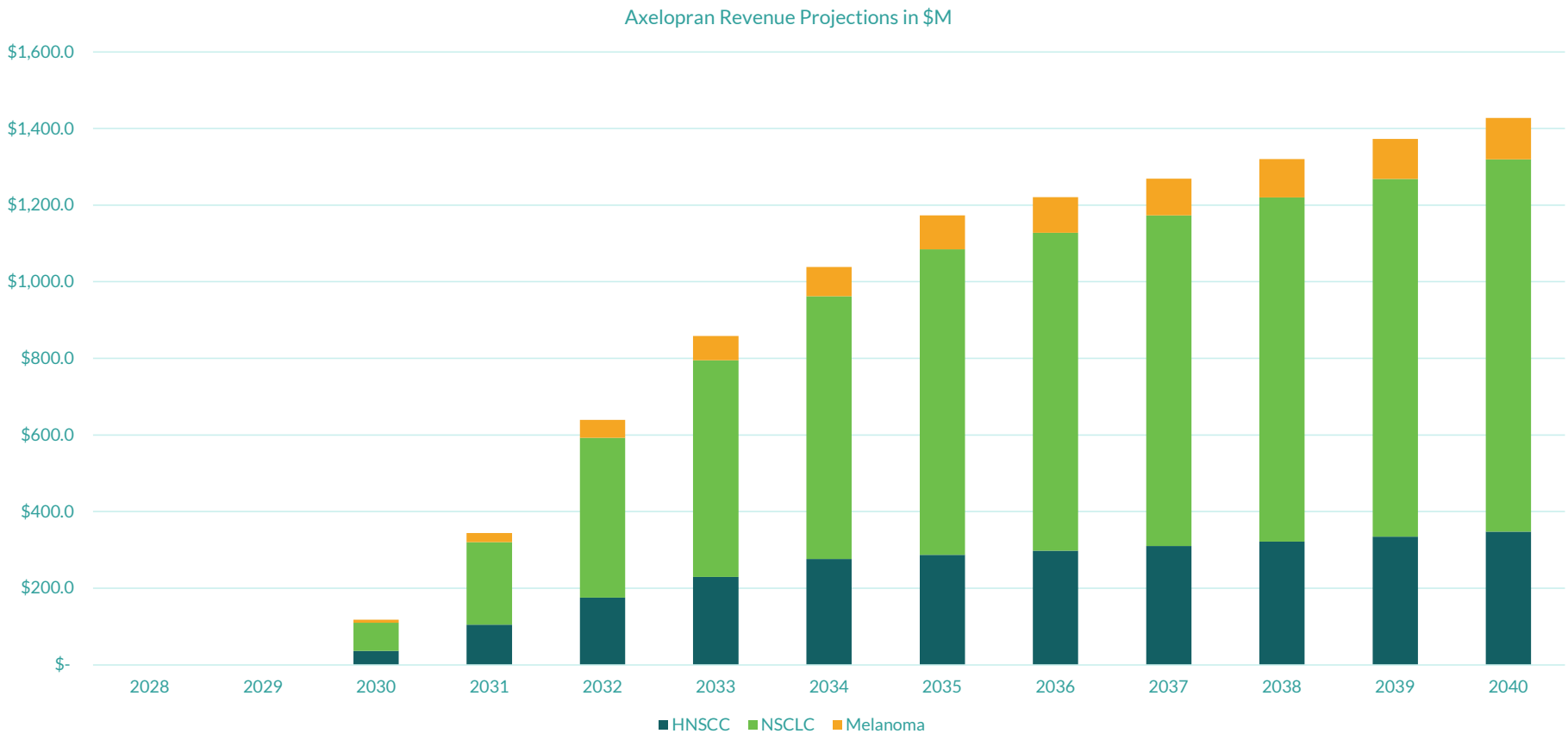
How Often Do We Use Opioids And ICIs Together?



Could Opioid Exposure Be Affecting Response Rates?



Financial projections



Executive Summary

Glycyx

What

- **Axelopran prevents opioid-induced immunodeficiency**: clinic-ready asset in immuno-oncology
- **Established tolerability:** safety database of >550 patients and clinical collaborators ready
- **Phase 2a basket study:** clinical development in solid tumors with opioid + ICI use

Why

- **>50% decline in ORR:** patients taking opioids with ICI halve their respective response rate
- **Large market:** On average, >45% of immunotherapy patients take immunosuppressive opioids
- **No current competition**: Axelopran set to be first-in-indication asset

How

- **Raising $30M in Series A funding**
  - Complete Phase 2a basket trial in solid tumors
  - Secure full ownership of asset via minority inventor buyout (Theravance)
  - Convert pipeline of BD opportunities following Phase 2a data