SPEXIS

Generating Hope for Rare Disease & Oncology Patients

January 2024

Non-Confidential

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The Spexis Proposition:

Life-changing macrocycle therapeutics for rare disease and oncology patients

Macrocycle focus:
- Extensive macrocycle platform with both peptidic & non-peptidic libraries
- 3 clinical-stage products discovered in-house thus far
- Lead asset ColiFin®: approved (in EU), US Phase 3-ready, also a macrocycle
- Significant molecular glue & protein degrader potential

Early & late-stage cystic fibrosis (CF) pipeline:

Funded and supported by the CF Foundation & IMI

ColiFin®:
- Lead candidate for CF
- EU approved; U.S. Phase 3 ready

1 in-house

Inhaled Murepavadin:
- Novel OMPTA-antibiotic
- 9 i.v. clinical trials in ~290 subjects to date
- Phase 1 CF trial data reported in Jan 2023

2 in-house

Balixafortide:
- Best-in-class CXCR4i
- 8 clinical trials in >500 subjects to date
- Now under development for pancreatic cancer

3 in-house

Lonodelestat:
- Best-in-class neutrophil elastase inhibitor
- Phase 2 ready
- Out-licensed to Santhera

Excellent value growth potential:
- Lead asset highly de-risked
- Multiple other clinical shots-on-goal
- Cutting-edge macrocycle platform

IMI – Innovative Medicines Initiative (EU research initiative)

Spexis' Focus on Macrocycles

Broadly Applicable, Large Clinical Data Set, Partner Validated

Macrocycles

- Can target **difficult-to-drug extra- and intracellular structures**
- **Offer unique drug-like profiles** incl. favorable PK/PD parameters, improved oral bioavailability, enhanced metabolic stability and cell permeability[1]
- Since 2014, **19 macrocyclic structures approved by FDA**[1]

Extensive peptidic & non-peptidic libraries, databases & IP

Will fuel pipeline and generate partnering opportunities

- **2 in-house candidates progressed through P3 thus far; additional 1 (ColiFin®) in-licensed & P3-ready**
- Additional candidate out-partnered & entering P2
- Validated by multiple prior **pharma collaborations**

FOSUN PHARMA

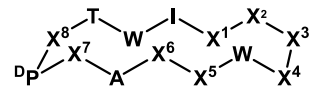
santhera

10k – 200k MW
Biologics

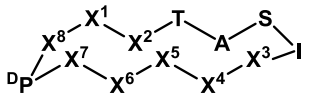
Spexis Macrocycles
500 - 2'000 MW

100 – 500 MW
Small Molecules

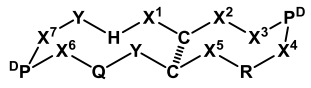
Murepavadin



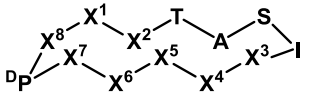
Lonodelestat



Balixafortide

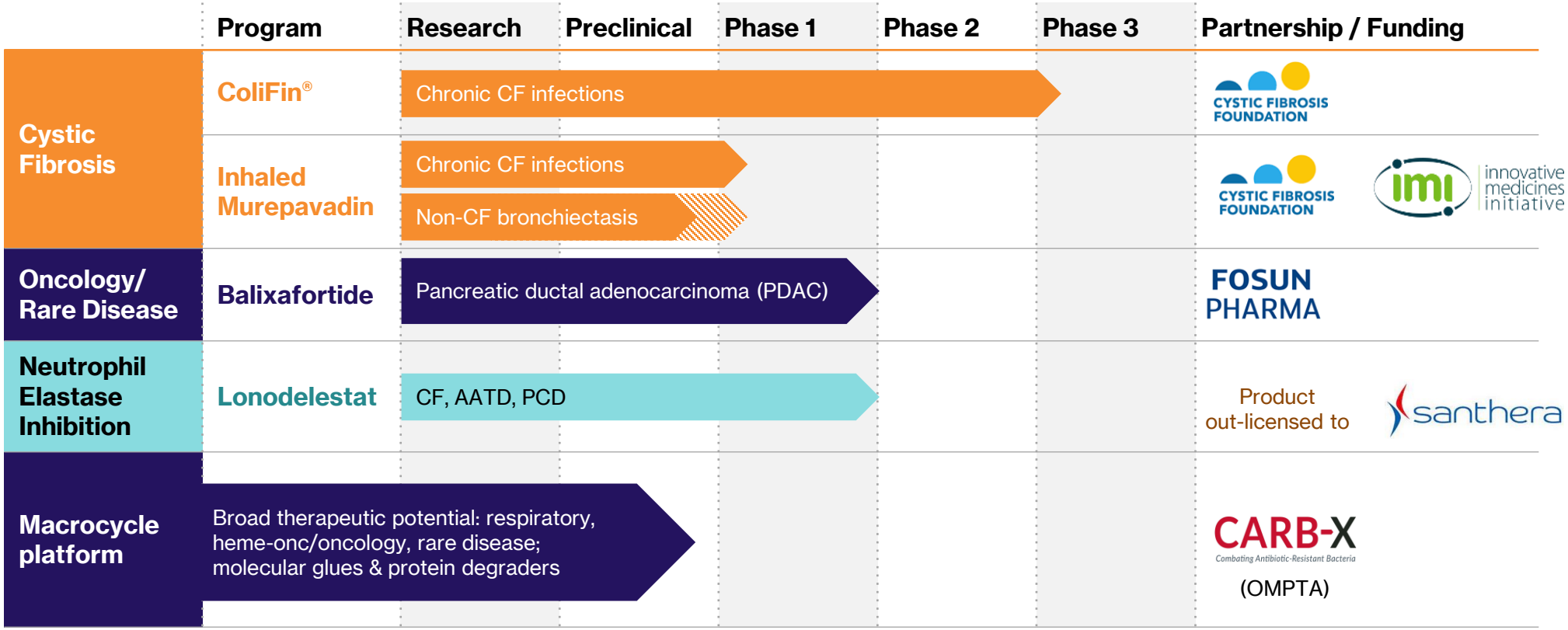


New Candidates



1 https://doi.org/10.3390/molecules27031012

Spexis Pipeline: Multiple "Shots-On-Goal"
Potential for Significant Value Generation



Pipeline Today Readiness if/when initiated

CF – cystic fibrosis; AATD – alpha-1 antitrypsin deficiency; PCD – primary ciliary dyskinesia
OMPTA – Outer Membrane Protein Targeted Antibiotics
Indications according to https://www.santhera.com/health-care-professionals/lonodelestat

ColiFin®:

As Approved In Europe

ColiFin®

Significantly De-risked Via EU Approval, FDA Interactions & CF Foundation ("CFF") Support

Approved in EU (DE, AT, CH, FR, SP, IT, UK, NE): 2010 – 2018 via decentralized process

U.S. Phase 3 Program ("COPA"):

- FDA "Study May Proceed Letter": 1 Phase 3 trial sufficient
- QD dosing favored due to high treatment burden in CF patients
- Continuous use therapy (not 28d on, 28 off): same as ColiFin® EU label, also significant compliance factor
- COPA developed with CFF equity investment & sig design input & endorsement from CFF's Therapeutics Development Network – a "must have" for doing CF trials in U.S. and Canada

Multiple P3 "COPA" study value-inflection points:

1st Interim Analysis ("IA") :
- 1x/day dosing safety/PK/efficacy readout after ~80 subjects

2nd Interim Analysis
- after 60% of subjects have completed COPA Part A
- **if positive, could file early NDA**

Commercial:

QIDP + Orphan Drug designation = 12 yrs U.S. market exclusivity

Concentrated N. American market: ~130 CF care centers

Small commercial structure sufficient to "go-it-alone"

Future ColiFin® Patients Already Use Inhaled Colistin

Current EU Usage

- EU inhaled colistin revenues (all products) **est. €75M/yr**
- Average EU price per course: €800-1.5K[1]

EU vs. US

- **US pricing 3-5x EU** (e.g. TOBI®, Cayston®, generics)
- EU29 & US CF patient population comparable (~40K vs 30K)

Current US Usage

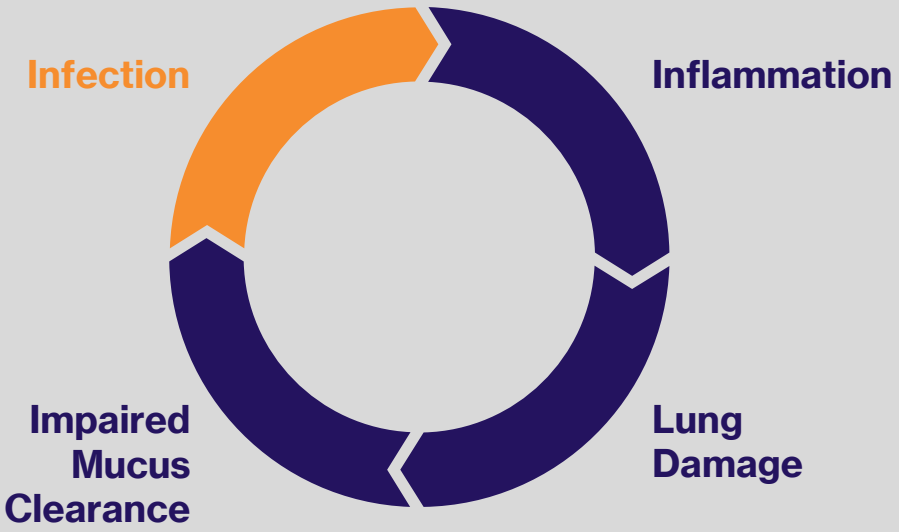
- ~2200 CF patients used unapproved colistin in 2019[2]
- Those patients **will** convert to ColiFin® upon approval[3]
- Reaching **only** those patients :
  - **Projected revenues: $80M**
- >8,000 add'l US adults w/ mod /adv disease, many cannot access unapproved colistin

EU-like penetration @ US pricing:
- **Projected US revenues: $180-$280M**

[1] Confidential market information shared
[2] 2020 CFF Registry Report, last year pre-COVID disruption
[3] TOBI® & Cayston® predated by unapproved versions. Both rapidly captured those markets

CF Chronic Infections Promote Lung Damage Progression

Increasing Need for Inhaled Antibiotics



85 % of eligible population receive CFTR modulators – slowing disease progression & improving mucus clearance[1]

5yr data show reduced load BUT chronic infections persist – will remain major issue[2]

- **Ageing CF patient population – a longer, but not healthier life[1]**
- **Chronic lung infections – increased likelihood as patient ages; *P. aeruginosa* predominant ≥ age 33[1]**
- **Increasing need for long-term inhaled antibiotics[1]**

1) https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf;
2) Finke et al; Lenhan et al; Quinn et al.

ColiFin®: Potential to be More Effective, Safer Therapy

Current Treatments in U.S. Not Fully Addressing Need

	TOBI®/Cayston®	ColiFin®
Mechanism of Action	Leads to resistance development	Difficult for *P. aeruginosa* to mutate around
Resistance Development	Increasing, up to 40 % in some regions[1,2]	Rarely exceeding ~5 %[1,2]
Safety	TOBI has significant ototoxicity concerns	Validated in EU: Strong efficacy, minimal serious adverse events in >15K patients dosed to date
Efficacy	Decreased efficacy over time	
Dosing	Continuous b.i.d./t.i.d. alternating therapy ("CAT") (rotation of 28d cycles)	Continuous (i.e., no CAT) b.i.d. dosing with P3 plans for q.d. dosing

Colistin available as I.V. formulation – inhalation unapproved (U.S.)
→ not reimbursed, most patients must pay-out-of pocket

1) doi: 10.1128/AAC.01541-19
2) doi: 10.1128/AAC.02483-20

ColiFin® Life Cycle Management:

Expansion into Non-CFBE, COPD

Non-CF Bronchiectasis & COPD patients also suffer chronic *P. aeruginosa* infections, no proven inhaled standard-of-care

An effective QD ColiFin® would be an attractive therapeutic in both these additional indications

LCM Expands Treatable Patients to >30M Worldwide

3 COPD
50x U.S. CF Market

- 15M US Patients, >250M globally
- 5-15% infected with *P aeru* [4]
- Infections drive exacerbations, deaths

2 Non-CF Bronchiectasis
15x U.S. CF Market

- 1/3rd of patients have 3+ exacerbations/yr [1]
- Most of these have chronic lung infections
- ~30% culture *P aeru*, have worse outcomes [2,3]

1 Cystic Fibrosis
~10K Treatable US Patients

- Primary indication w/ front-line label
- Very accessible patient population
- Established usage in U.S. & RoW

1) McShane et. al. 2013, DOI: 10.1164/rccm.201303-0411CI
2) Finch S et. al. 2015 DOI: 10.1513/AnnalsATS.201506-333OC.
3) Chen et. al. 2018, DOI: 10.1080/13543784.2018.1439919
4) Planquette et. al. 2015, DOI: 10.2147/COPD.S71413

Potential ColiFin® Peak Revenues

Product	Indication	Territory	Target Patient Population	Peak Penetration	Revenue per Patient/Yr	Projected Revenue
ColiFin®	CF	US	12,000[1]	45%	$36K	$210M
	nCFB	US	50,000[2]	30%	$30K	$450M
		Asia Pacific	250,000[3]	20%	$10K	$500M
Subtotal						**$1,160M**

[1] Adult US patients with moderate to advanced disease, per CFF registry report
[2] 450K nCFB patients, 37% exacerbate 3+ times/yr, ~30% of those culture P aeruginosa (Chalmers 2018)
[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9066779/, https://pubmed.ncbi.nlm.nih.gov/25542602/, https://erj.ersjournals.com/content/54/2/1900194

ColiFin® Target Patient Populations & Value Generation
Compares Well to Insmed's ARIKAYCE®

	ARIYAKCE®		ColiFin®	
Indication	**MAC NTM (Refractory)**	**MAC NTM (1st Line)**	**CF**	**nCFB**
Regulatory Status	**Approved**	P3 readout	P3-ready	TBD
Target Patient Population (US)	10-15K *(Insmed est.)*	75-100K *(Insmed est)*	~40K CF Patients ~12K eligible	~450 nCFB Patients ~50-70K eligible
Other Markets	JP: 15-18K *(Insmed est.)* EU: ~1K *(Insmed est.)*	JP: 60-70K *(Insmed est.)* EU: ~4K *(Insmed est.)*	-	~80K EU eligible ~250K APAC eligible
Net Revenues	**~$300M *(2023 est)***	~$800M Peak *(analyst estimates)*	~$200M US *(projected peak)*	$100M US (*proj. off label)* $500M+ (*on label)*
Company Mkt Cap:	**$1.5B** *(post-2018 approval)*	**$4.28B** *(now, post-positive 1st line P3 readout 5 Sep '23)*		

ColiFin® Phase 3 Program: COPILOT Trial

QD vs BID dosing, open label

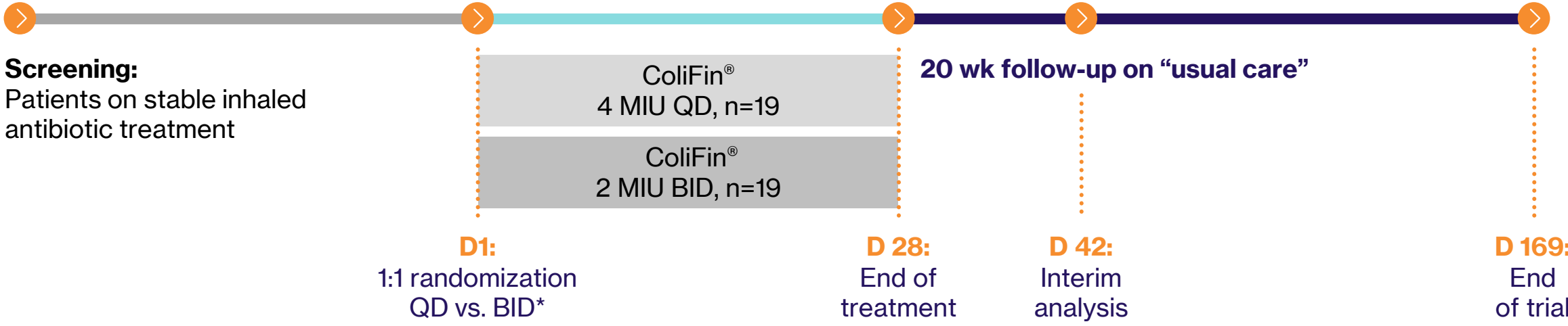
Primary Objective:

- Tolerability and safety of ColiFin®, once-daily (QD) vs twice-daily (BID)
- Interim analysis (Day 42) to support switch from BID to QD dosing in COPA
- Important short-term value inflection point: QD approval could grant USP

Secondary Objectives:

- Assessment of pulmonary function (ppFEV1)
- Clinical events (number/severity of pulmonary exacerbations, hospitalizations)
- Additional antibacterial therapy

To be conducted in Europe; enrollment expected to initiate 2H2023



* Stratification by current use of oral corticosteroids > or <= 10 mg QD or 20 mg QOD (prednisone or prednisolone equivalents)

ColiFin® Phase 3 Program: COPA Pivotal Trial

28d double blind efficacy + 20w open-label safety

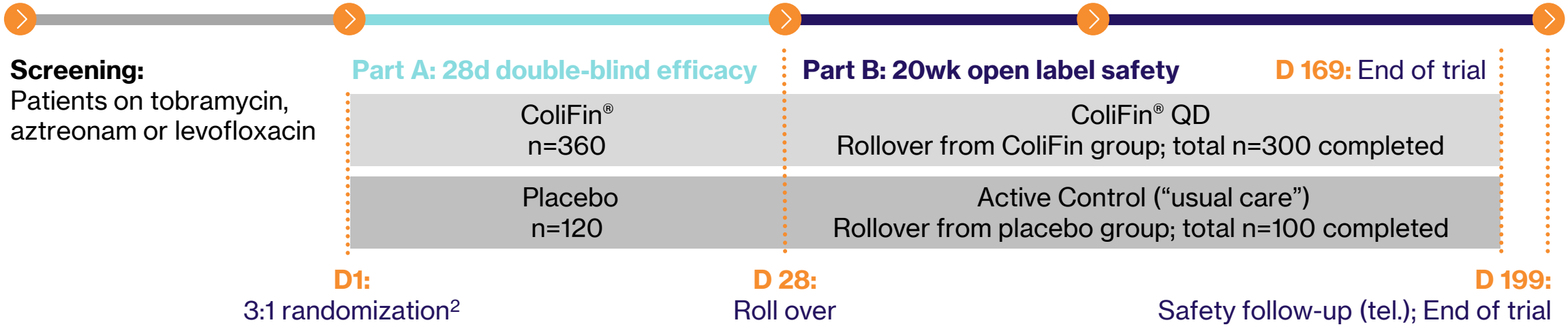
Eligible: Adults/adolescents with CF + chronic *P. aeruginosa (Pae)* lung infection

Therapy: Continuous ColiFin® for 6 months vs. placebo + usual inhaled antibiotics

Primary endpoint: Mean absolute diff. in ppFEV1[1] (of ≥3 %) in change from baseline to Day 28

Key secondary endpoints throughout 6 months: Difference in CFQ-R respiratory symptom score; exacerbation severity/duration; consistency of treatment response; sputum microbiology: *Pae* density, resistance development (MIC)

Independent Data Monitoring Committee: Interim efficacy analysis after 288 patients complete 28d days of treatment (~12 mos from FPI)



1) ppFEV1: Percent Predicted Forced Expiratory Volume in 1 second
2) Stratification of randomization by age (<18, >18 yrs, pp FEV 1 (<70 %;>70 %), prior PEx treated with systemic antibacterials in last 12 months, stable baseline use of CFTR modulators

Inhaled Murepavadin ("iMPV") for Cystic Fibrosis

Novel Class Therapeutic For a Rare Disease

Attractive market

- Peak CF sales 200-400m USD
- Label expansion potential to nCFBE: >$1B market

Phase 1a

- Clean safety demonstrated

Externally validated & partially funded

- Substantial funding from: EU Innovative Medicines Initiative (IMI) for Ph. 1a & CF Foundation for Ph. 2

High safety margin

- 9 clinical trials of IV MPV totaling 290 subjects have informed & de-risked the inhalation route
- Low systemic exposure upon inhalation mitigates nephrotoxicity risk
- High safety margin (5- to 10-fold above IV) in GLP tox studies

IP protected

- Market exclusivity through about 2036 via COM/additional IP
- Eligible for QIDP & orphan drug status

Balixafortide: Potent CXCR4 inhibitor

Applicable to wide range of oncology and rare disease indications

Balixafortide

- Potent, highly selective blocker of CXCR4
- CXCR4 is involved in tumor growth and metastasis and is also implicated in a variety of primary immune deficiency and other rare diseases

Clinical proof of concept established

- >500 patients in 8 clinical trials
- Phase 3 study in advanced HER-2 negative breast cancer did not achieve primary endpoint; data analyses ongoing

Good safety and tolerability profile

- Well tolerated by i.v. route of administration
- No limiting safety events identified at top dose given (5.5mg/kg)
- Shown to overcome SoC drug resistance
- Compatible with combination therapies

Pursuing new indications

- **Encouraging results of BLX + anti-PD1 in multiple animal models of pancreatic ductal adenocarcinoma (PDAC)**
- Extensively profiled in animal models of stem cell mobilization, cancer, inflammatory and rare disease indications

Pancreatic Cancer

Multi-Billion $ Indication w/ High Unmet Need

3rd leading cancer death (US)
Projected **2nd** by 2030[1]

~500k annual diagnoses ww[2]

~470k annual deaths ww[2]

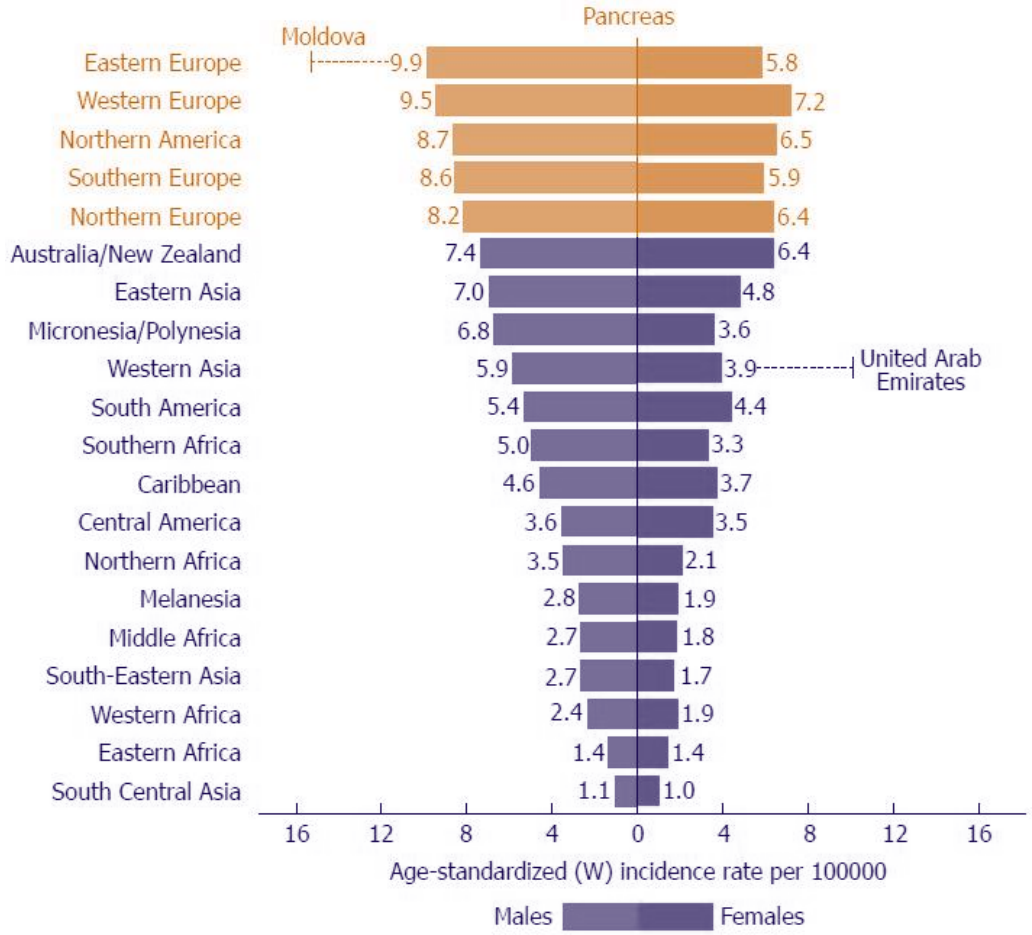
6% 5-yr survival for pancreatic ductal adenocarcinoma (PDAC)[4]

USD 6.85 Billion
projected market by 2029[3]

[1] Rahib L et. al, Estimated Projection of US Cancer Incidence and Death to 2040. *JAMA Netw Open*. 2021;
[2] World J Gastroenterol., Irena Ilic et al., 2022 Aug 28; 28(32): 4698–4715
[3] https://www.globenewswire.com/en/news-release/2023/02/20/2611273/0/en/Pancreatic-Cancer-Treatment-Market-Exhibits-15-7-CAGR-to-Hit-USD-6-85-Billion-by-2029.html
[4] Yushifumi Noda et al., Medical Imaging, 22, Article number: 23 (2022)

PDAC Patients Are Being Left Behind

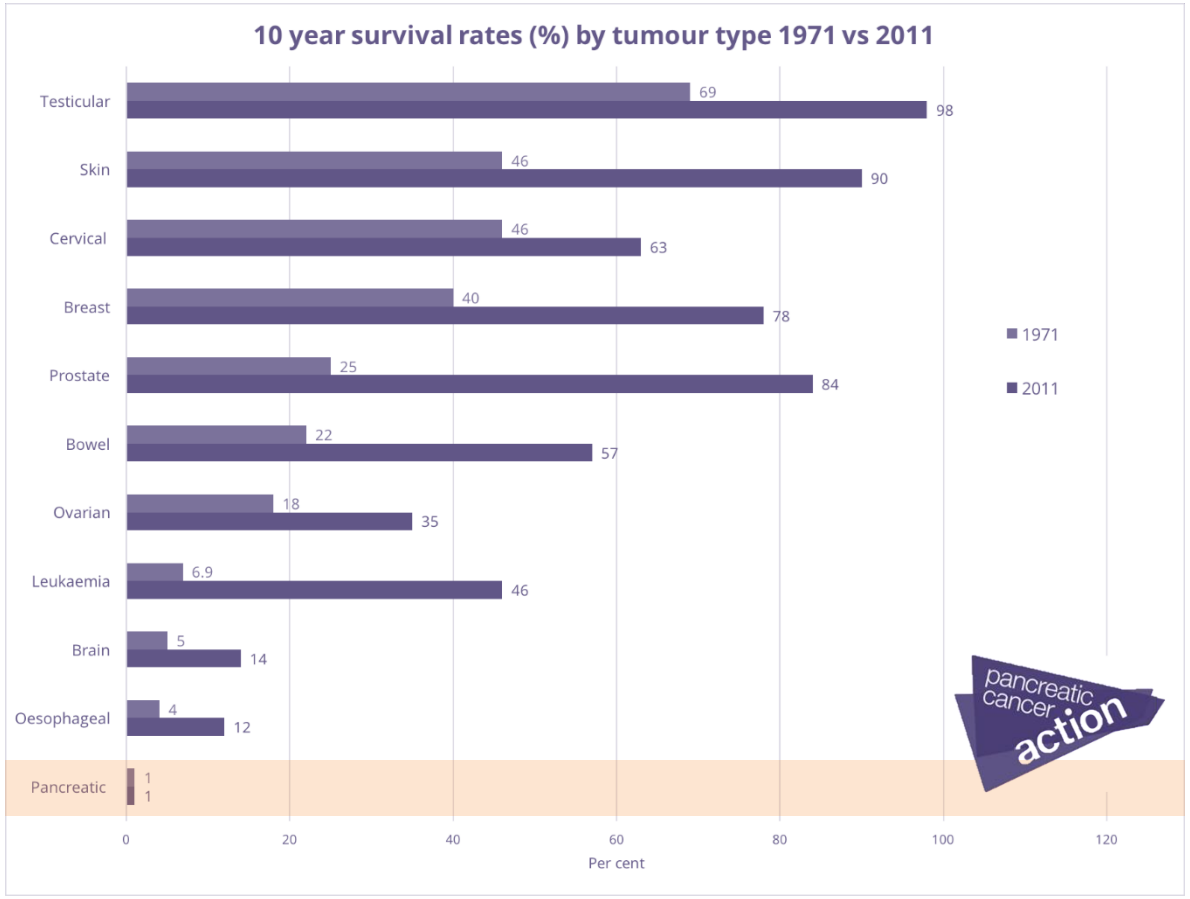
- Pancreatic Ductal Adenocarcinoma accounts for ~90% of all pancreatic cancers[1], but:
  - Survival rates are the lowest of all common cancers
  - Only ~15% have operable disease at diagnosis
- Global incidence highest in Europe, North America[2]



[1] doi: 10.4103/eus.eus_60_17
[2] doi: 10.3748/wjg.v24.i43.4846

PDAC Patients Are Being Left Behind

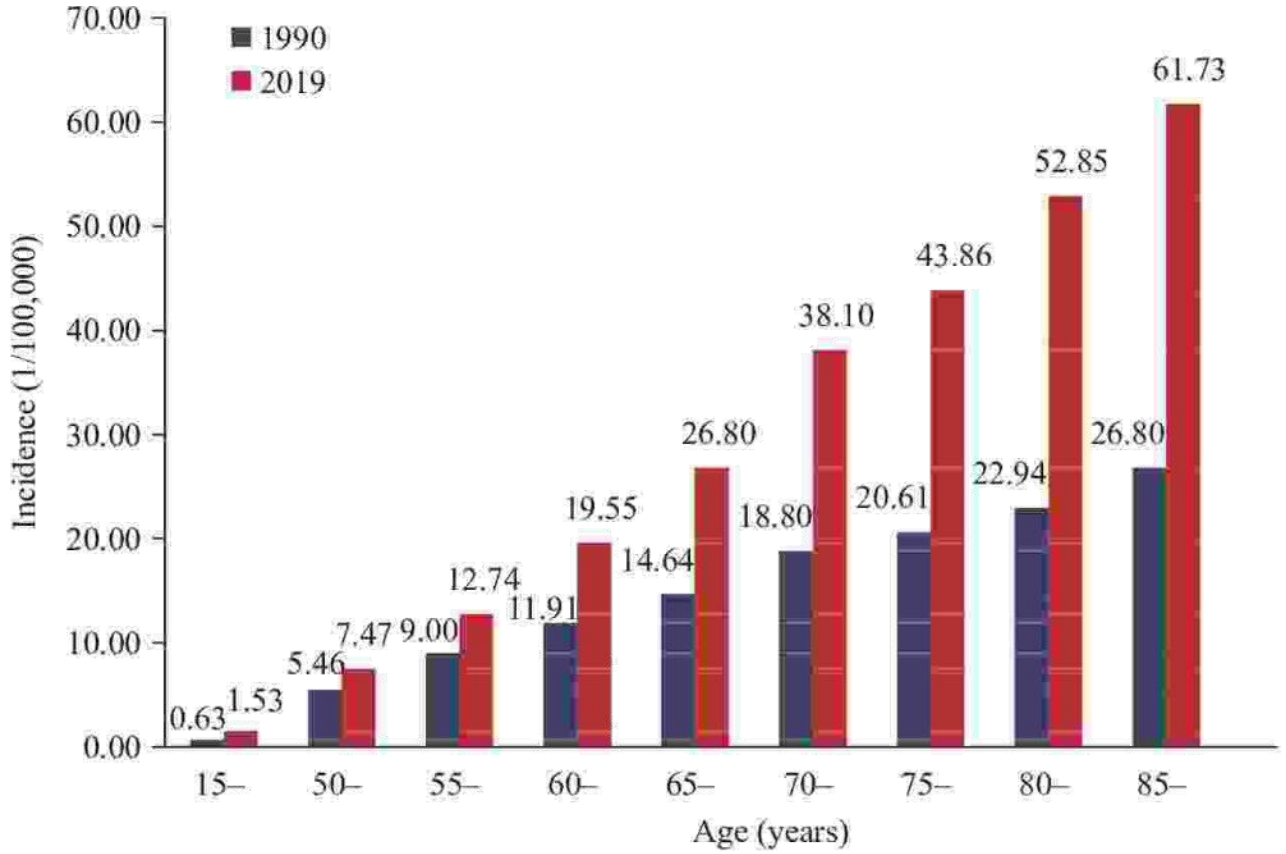
In last 40 years, 10yr survival rates have dramatically improved for every cancer **except pancreatic**



Recently approved therapies (e.g. Abraxane) have **increased 5-year survival only slightly (~12%)**

[1] pancreaticcanceraction.org

Incidence of Pancreatic Cancer in China Has Increased Significantly Over The Years



Increasing incidence of pancreatic cancer in China[1]:

- In 2019, the number of pancreatic cancer cases in China was estimated to be **114,964** and the incidence was estimated to be **5.78/100,000**, an increase of 329.40% and 82.11% compared with 1990, respectively.
- Whether in 1990 or 2019, the incidence of pancreatic cancer was low before the age of 50, and it substantially increased with age, starting from the 50–54 age group, and reaching its peak in the 85-and-over age group
- The incidence for males is greater than that for females

There were 124,994 new cases of pancreatic cancer and 121,853 deaths in China in 2020[2]

[1] Yuan He et al., China CDC weekly, 2022, 4(24): 527-53 1
[2] IARC Global Cancer Observatory

Potential for Anti-PD1 in PDAC

Anti-PD1

Balixafortide

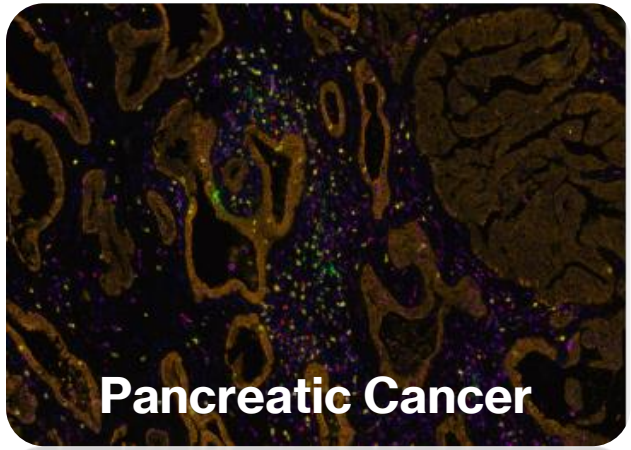
- PD-1 inhibitors have been most successful class of immuno-oncology agents
- Blocks mechanism by which many cancer cells suppress immune response

KEYTRUDA® (pembrolizumab) Injection 100 mg	2022 Revenues: **~$20.9B**	Approvals in melanoma, NSCLC, HNSCC, cHL, PMBCL, others
OPDIVO® (nivolumab)	2022 Revenues: **~$8.2**	Approvals in melanoma, NSCLC, KC, LC, CRC, melanoma, others
LIBTAYO® (cemiplimab-rwlc) Injection 350 mg	2022 Revenues: **~$445M**	Approvals in NSCLC, CSCC, BCC, others

- **However, PD-1 inhibitors alone have not shown significant survival benefits in PDAC**

[1] doi: 10.1016/B978-0-12-411638-2.00002-1

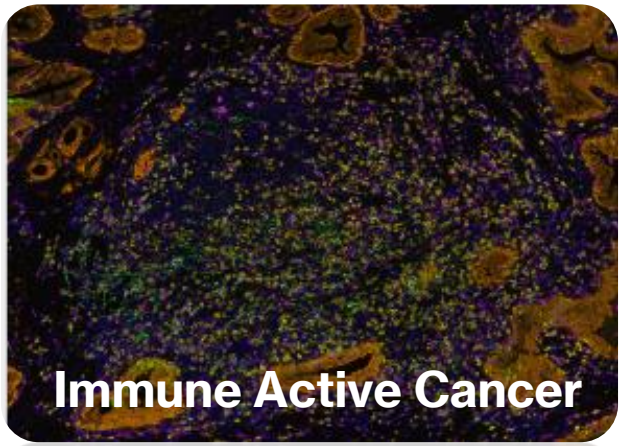
Immune Checkpoint Inhibitors (ICIs) Bring Survival Benefits, But Much Less Effective in PDAC to Date



⇦ **PDAC has:**

- Lower PD-1/PDL-1 expression **(green)**
- Lower CD8 expression **(yellow)**
- More FOXP3+ Treg cells **(red)**

Osipov Lab pending publication



Additional Issues with ICIs in PDAC[1]:

- PDAC is immunologically “cold” cancer: less T-cell infiltration, which ICI needs
- PDAC creates highly immunosuppressive tumor microenvironment (TME)
- PDAC often has dense stromal tissue barrier, acts as physical barrier

[1] doi: 10.1186/s12964-021-00789-w

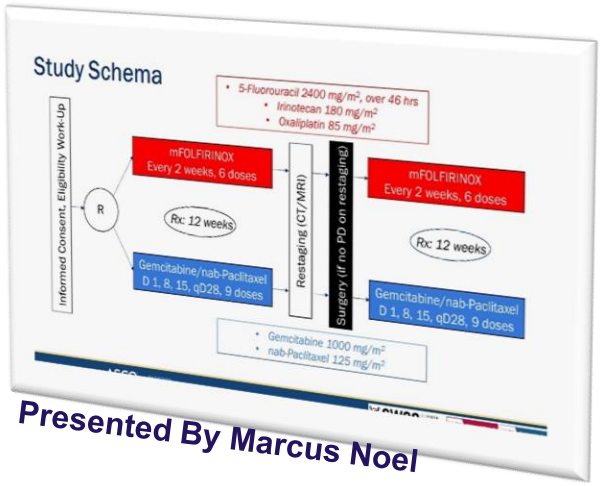
Potential for Anti-PD1 in PDAC

Anti-PD1

Balixafortide

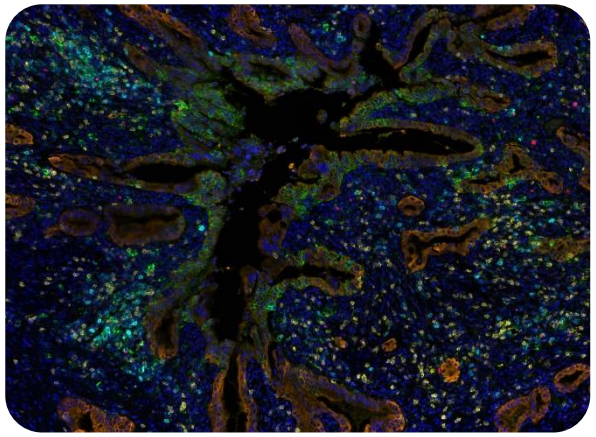
- However, recent studies suggest PDAC mutates to use PD-1 in response to chemotherapy

SWOG S1505: Results of Perioperative Chemotherapy with mFOLFIRINOX vs Gemcitabine/nab-Paclitaxel for Resectable Pancreatic Ductal Adenocarcinoma



Presented By Marcus Noel

- PD-L1 induction observed on tumor epithelium following neoadjuvant chemotherapy



Multiplex immunofluorescence staining of PDACs following neoadjuvant geme/abrax. CD 8 Yellow; FOXP3 Red; CD68 Magenta; PD-1 Cyan; PD-L1 Green; Keratin Orange; DAPI. Note that **PD-L1 expression (in green) on tumor epithelium was induced following neoadjuvant chemotherapy**

[1] doi: 10.1016/B978-0-12-411638-2.00002-1

Rationale for Balixafortide in PDAC

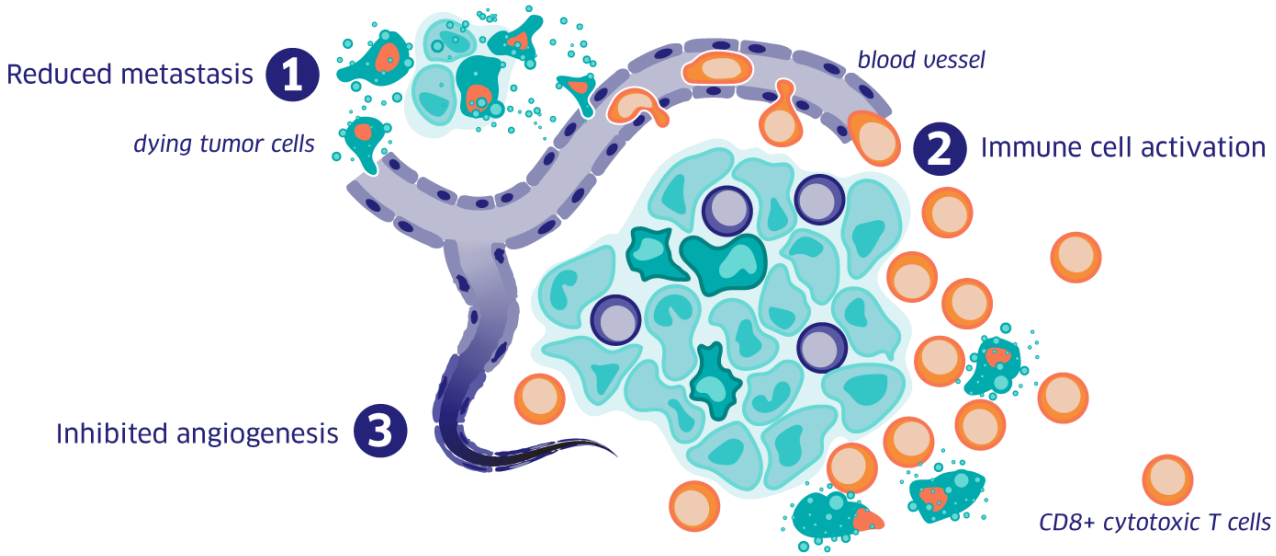
- CXCR4 is an alpha-chemokine receptor specific for stromal-derived-factor-1 (SDF-1)
- CXC4 overexpressed in 23 different solid tumor types, including pancreas[1]
- **Data to date shows:**
  - **PDAC patient CXCR4 expression negatively correlates with overall survival**
  - **Exceptional responders to PDAC chemotherapy have lower CXCR4 expression**
  - **CXCR4 inhibition potentiates Anti-PD-1 therapies in animal models**
- **CXCR4 could enable ICI treatment in PDAC**

[1] doi: 10.1016/B978-0-12-411638-2.00002-1

Summary of CXCR4i Mechanisms

Anti-PD1

Balixafortide



CXCR4 Inhibition Results in:

1. Reduced Metastasis:

- Fewer tumor cells into the circulation, fewer metastases
- Inhibition of epithelial-to-mesenchymal transition
- Reduction of tumor stemness

2. Immune suppression › Immune cell activation:

- Reduction of immunosuppressive cells (e.g., Treg, MDSC, cancer-associated fibroblasts)
- Increase of tumor-eliminating cytotoxic T cells

3. Inhibited angiogenesis:

- Smaller and less blood vessels in the tumor leading to reduction of tumor blood supply
- Preventing entry of endothelial progenitor cells and differentiation

Spexis Executive Management & Board of Directors

Highly Experienced Team

Jeff Wager, MD CEO & Chairman	30 yrs VC & CEO leadership; >$2.5B in value created since 2000
Martin Jakobovic Acting CFO	11 yrs finance experience in pharma and biotech
Juergen Froehlich, MD Consulting CMO	30+ yrs Chief Medical Officer & senior reg affairs experience
Dennis Ausiello, MD Vice Chair of the Board	17yrs Physician-in-Chief, MGH 8 yrs lead director of the Pfizer board
Kuno Sommer, PhD Director	Former CEO, Berna Biotech (acq. by J&J) Chairman Bachem, Sunstar, Targimmune, more
Robert Clarke, PhD Director	20+ yrs inhaled R & D and CEO experience
Dan Hartman, MD Director	25+yrs R & D leadership; Head of $2B Gates malaria R & D portfolio
Bernard Bollag, MBA Director	Senior finance executive across corporate finance & capital markets

Spexis

Near-term and multiple value inflection points

CF therapeutic proposition addresses important and growing need

Two CF/nCFBE clinical candidates

- ColiFin® – starting Phase 3 contingent on next financing or corporate partnership
- Inhaled murepavadin (iMPV) – positive Phase 1 data reported in Jan 23; back-up to ColiFin®

Balixafortide (BLX)

- 8 clinical trials to date; >500 subjects dosed; under evaluation for additional oncology & rare disease indications
- Pancreatic ductal adenocarcinoma (PDAC) now selected as next clinical development priority

Proprietary macrocycle platform poised to build pipeline and fuel corporate partnerships

- Result of >$400M prior investment & multiple alliances
- iMPV, BLX & lonodelestat generated by our macrocycle platform; ColiFin® (in-licensed from PARI) also a macrocycle
- Highly leverageable towards other extracellular, intracellular & protein-protein interaction targets
- Ideal for targeting protein-protein interactions, molecular glues and targeted therapies

SPEXIS

Hegenheimermattweg 125

CH-4123 Allschwil, Switzerland

Key Contact Information:

Website link	www.spexisbio.com
IR email	IR@spexisbio.com
Jeff Wager, M.D. **Chairman & CEO**	jeff.wager@spexisbio.com
Martin Jakobovic **Acting CFO**	martin.jakobovic@spexisbio.com