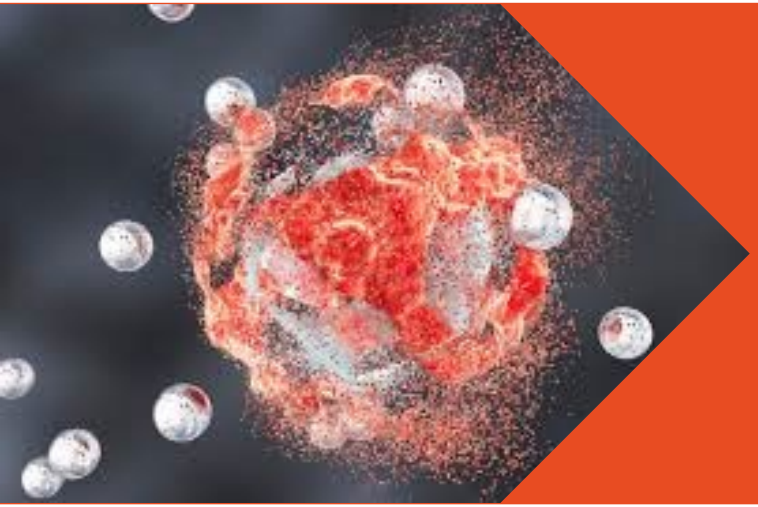

ONCOLOGY PORTFOLIO ACQUISITION STRATEGY FOR NCBB PHARMA

CAROLINA ADVISORY

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Executive Summary

Situation

Our client is NCBB Pharma, a US-based multi-national biopharmaceutical company. NCBB Pharma currently has an oncology portfolio and is looking to expand into biliary tract cancer (BTC) by acquisition of a late-stage asset.

Key Objective

Evaluate the opportunity associated with two promising assets in Phase 3 trials:

- **DUK-032:** Oral TKI targeting FGFR1-3 as a 1L monotherapy
- **UNC-023:** Oral IDH1 inhibitor for 2nd line treatment of cholangiocarcinoma.

Recommendation

NCBB Pharma should acquire

UNC-023

Projections

Acquiring UNC-023 will result in

$93.3M

Total Net Profit by 2032.

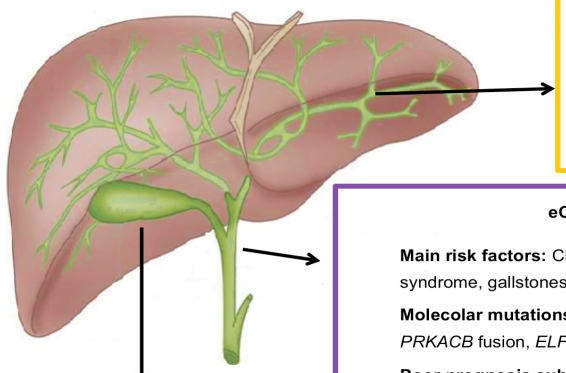
Framework

	Market size	Competition	Regulatory	Revenue Projection
DUK-032	✗	✗	✓	✗
UNC-023	✓	✓	✓	✓

UNC-023 has a favorable market size, competitive landscape, and revenue projection compared to DUK-032.

Biliary Tract Cancer: Overview

Disease Background



iCCA

Main risk factors: Cholangitis, obesity, diabetes, chronic hepatitis B/C, hepatolithiasis, Lynch syndrome

Molecolar mutations: *FGFR 1–3*, IDH 1/2, *BAP1*, *ARID1A* alteration, *EPHA2*

eCCA

Main risk factors: Cholangitis, Lynch syndrome, gallstones

Molecolar mutations: *PRKACA* or *PRKACB* fusion, *ELF3*, *ARID1B* mutation

Poor prognosis subtype with high immune checkpoint activity: *TP53, BRCA 1/2, PIK3CA mutation*

GBC

Main risk factors: Obesity, diabetes, chronic cholecystitis, gallstones

Molecolar mutation: *EGFR, ERBB3, PTEN, ARID2, MLL2, MLL3, TERT* promoter mutation, APOBEC signature

iCCA and eCCA (shared): *KRAS, SMAD4, ARID1A, GNAS*

Expected Outcomes

Median Overall Survival: 11.7 months
Median Relapse Free Survival: 8.0 months

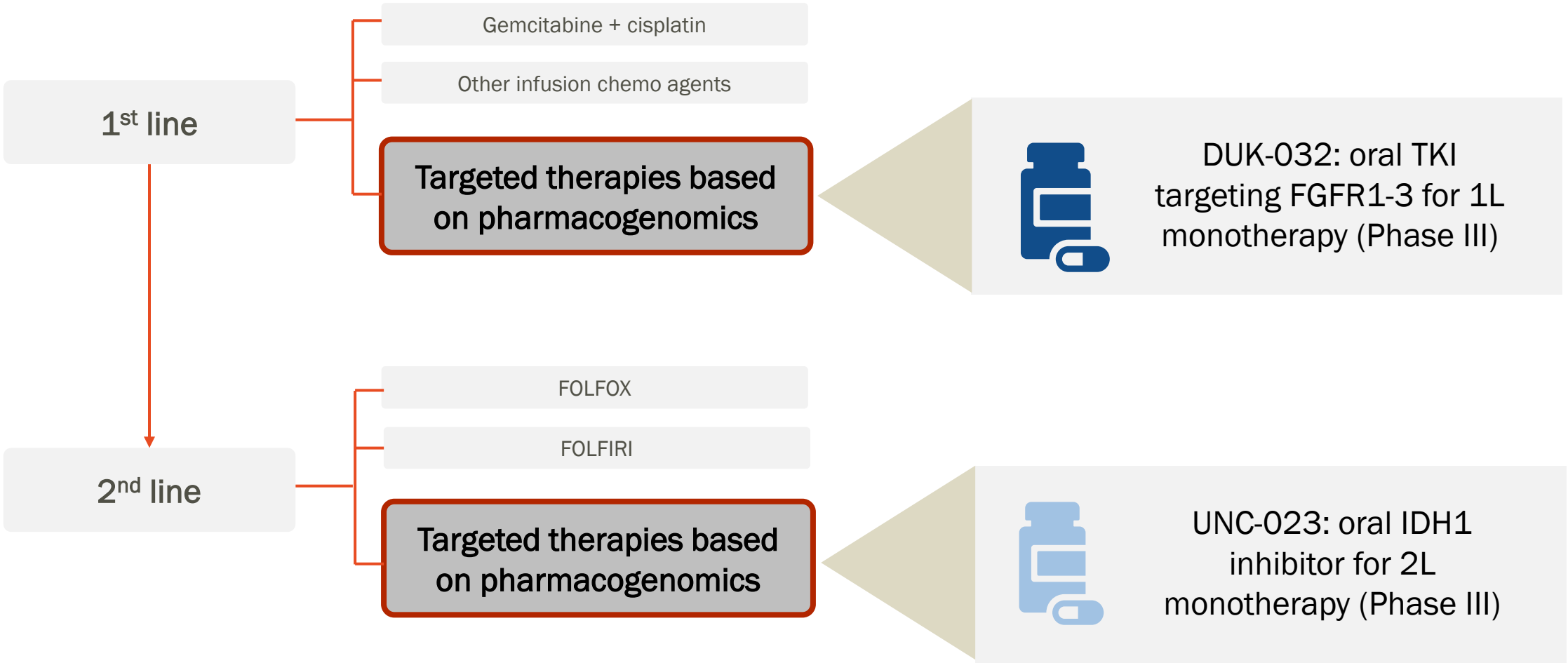
Chemotherapy Treatment Algorithm

- 1st line
  - Gemcitabine + cisplatin
  - Other infusion chemo agents
  - Targeted therapies based on pharmacogenomics
- 2nd line
  - FOLFOX
  - FOLFIRI
  - Targeted therapies based on pharmacogenomics

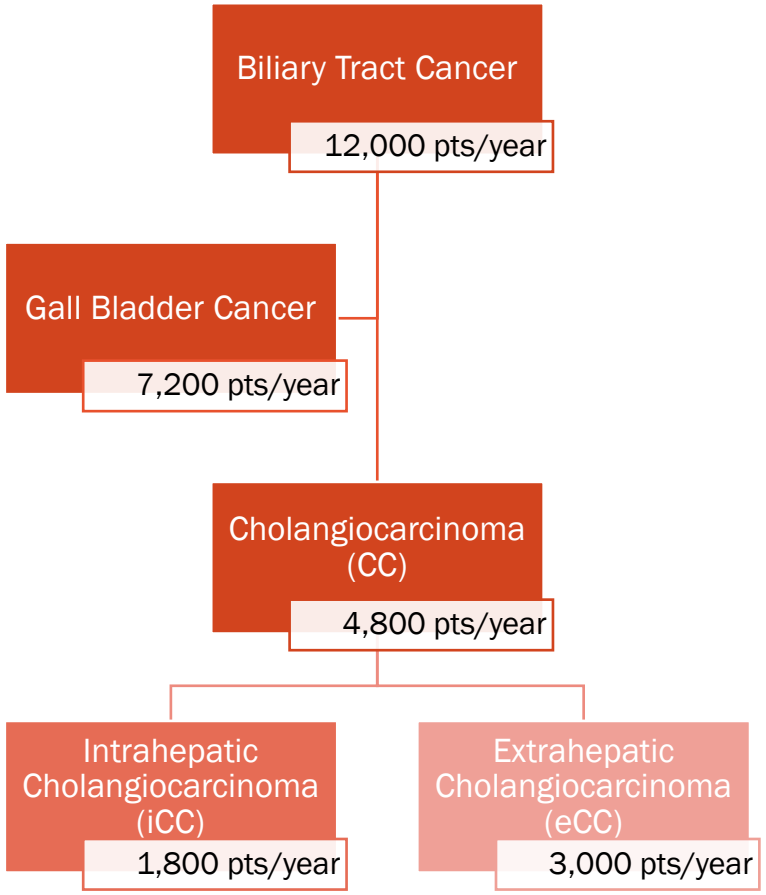
*FOLFOX: Folinic Acid, fluorouracil, and oxaliplatin
*FOLFIRI: Irinotecan, 5-fluorouracil (5-FU) and Leucovorin (LV)

* Banales, JM et al., Ghidini, M et al.,

Potential assets target different lines of therapy



Biliary tract cancer can be divided into three subtypes of cancer and by molecular mutation



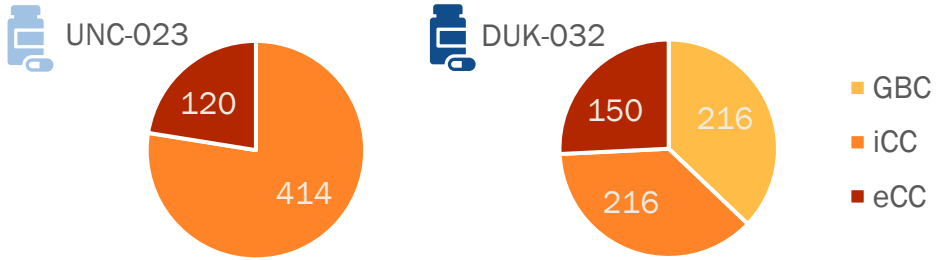
Percentage of BTC Patients with FGFR1-3 & IDH1 genetic mutations:

Mutation	GBC	iCC	eCC
FGFR1-3	3%	11 - 12%	0 - 5%
IDH1	0%	18 – 23%	3 – 4%

Trends in BTCs diagnosis rates:

GBC ↓ / iCC & eCC ↑

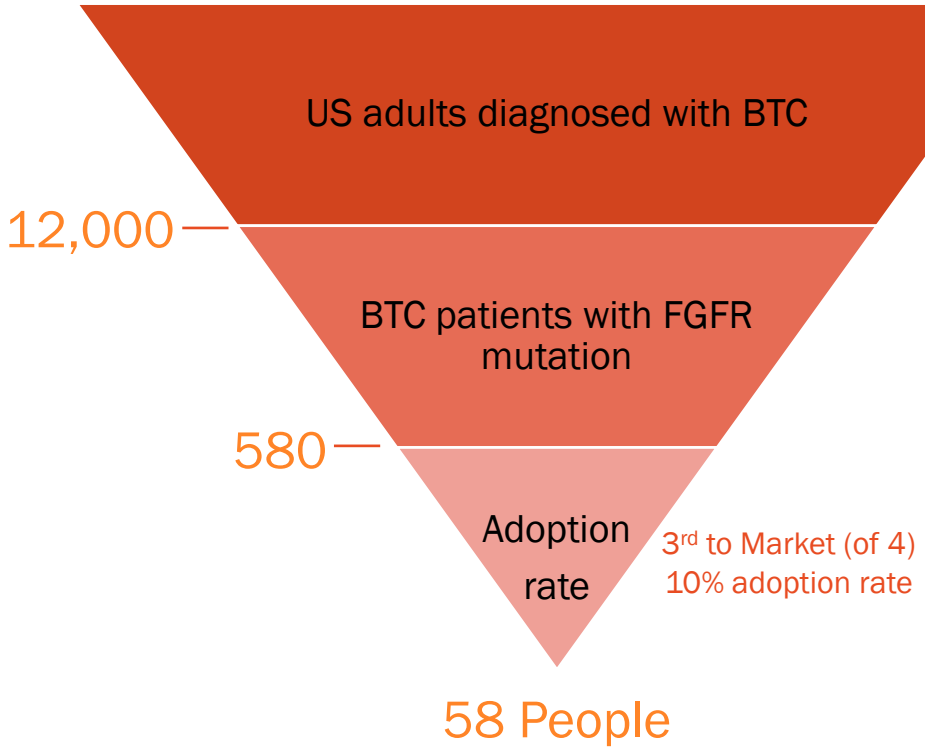
Patients that can be treated with UNC-023 and DUK-032 (by condition):



The trends in cancer diagnosis and genetic mutation prevalence are favorable for UNC-023.

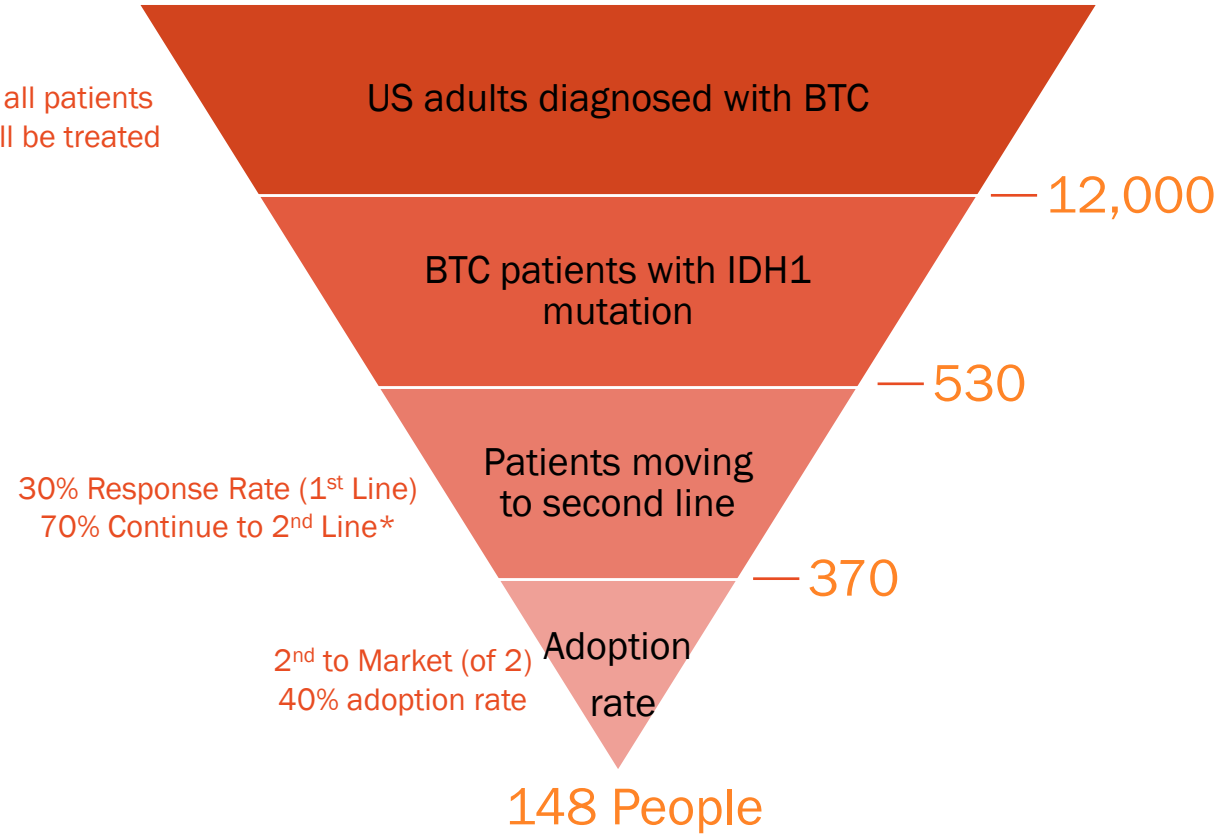
UNC-023 has a larger eligible patient population

DUK-032



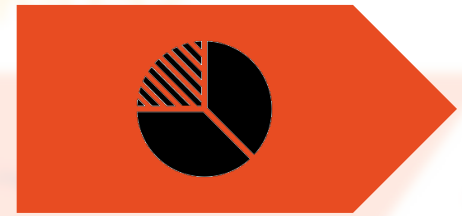
Assumption: all patients diagnosed will be treated

UNC–023



*Source (second line therapy): UpToDate, Systemic therapy for advanced cholangiocarcinoma

UNC-023 has a larger eligible patient population

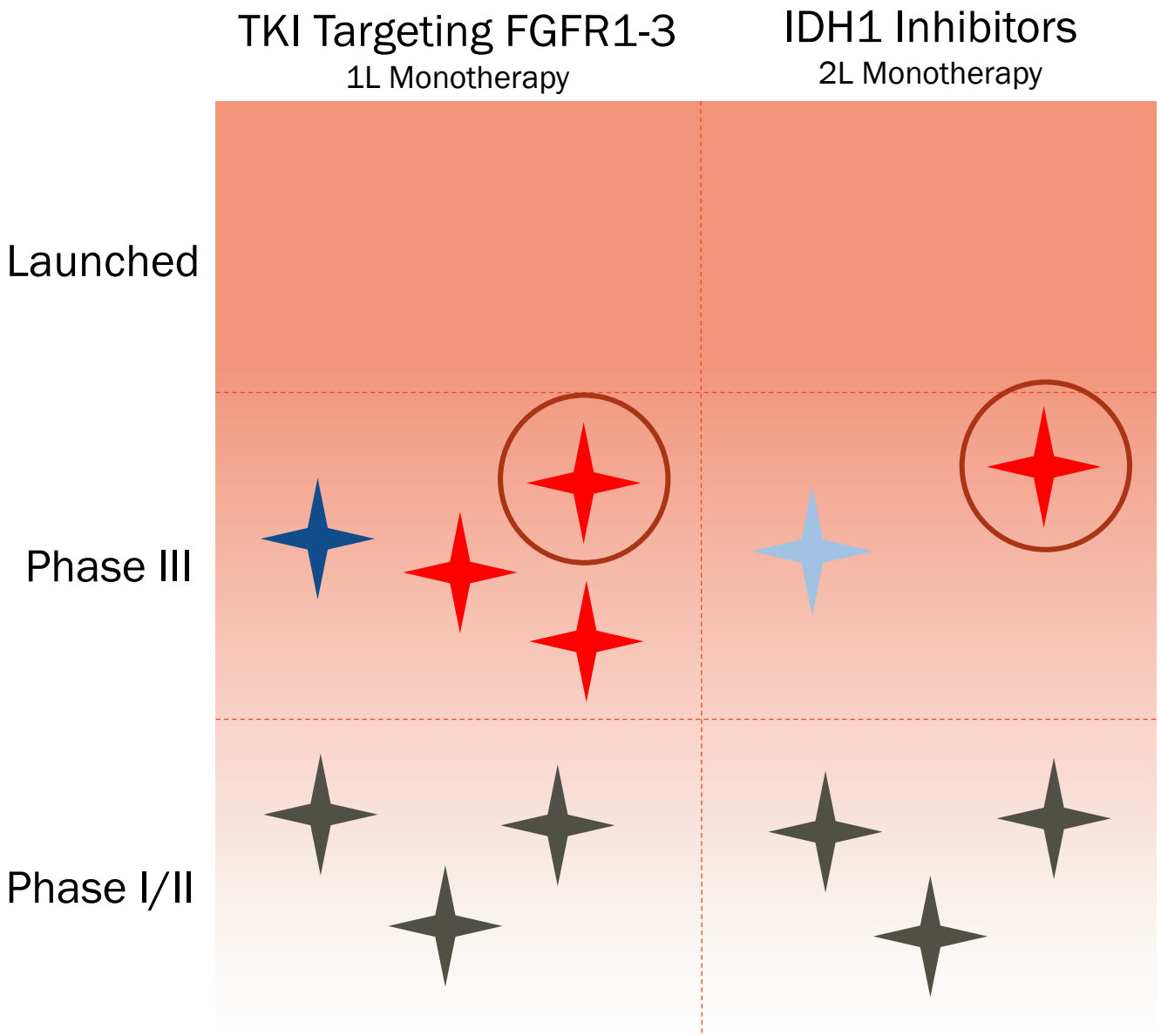


Market size

DUK-032	✗
UNC-023	✓

*Source (second line therapy): UpToDate, Systemic therapy for advanced cholangiocarcinoma

Competitive Analysis Favors UNC-023



DUK-032 faces tough competition from multiple drugs currently in Phase III, one of which is PEMAZYRE®

TIBSOVO® is awaiting FDA approval, and is the only current competition for UNC-023

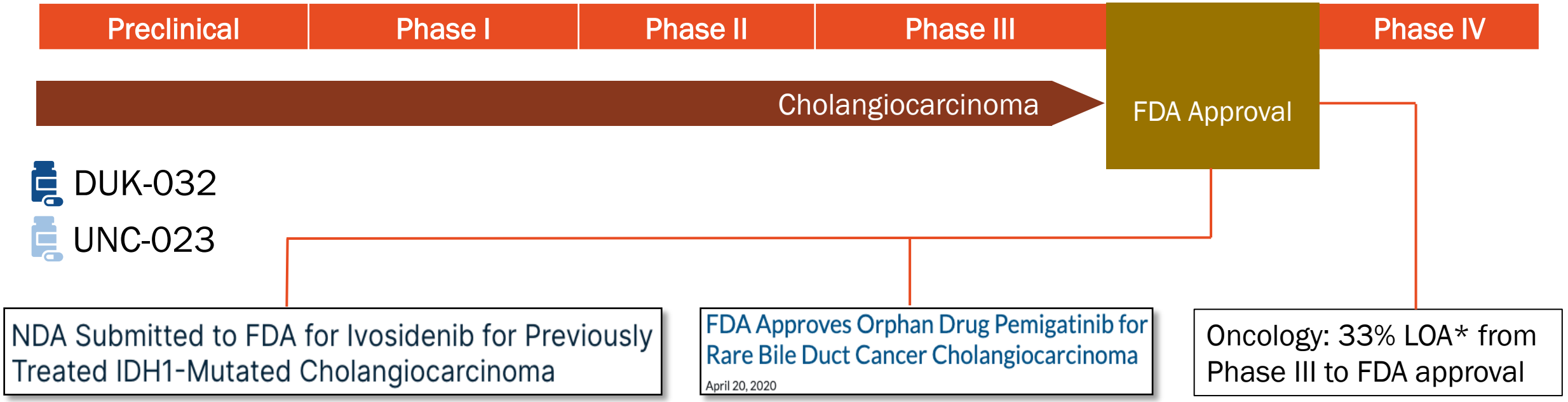
The potential market gain is much greater with UNC-023 due to its less direct competitive landscape

DUK-032
Main Competitors
UNC-023
Other Competitors

UNC-023 has a favorable competitive advantage

	Market size	Competition
DUK-032	✗	✗
UNC-023	✓	✓

Both assets face similar regulatory trajectory



Expedited Approval Process Potential

- Could qualify for **priority review** for both assets depending on phase III data
  - FDA takes action on NDA in 6 months compared to current average of 1.1 years in oncology

Orphan Drug Status Considerations

- US: <200,000 patients
- Seven years of **market exclusivity** from FDA approval
- Just over half of the unprotected products have faced competition, even decades after the lapsing of exclusivity

*LOA: Likelihood of approval

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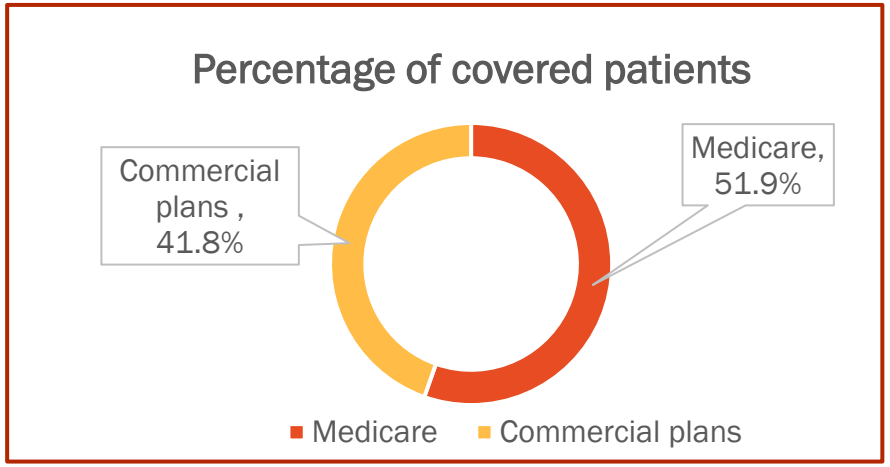
*BIO Clnical Development Success Rates 2006 – 2015., Orphan Drugs in the United States: Exclusivity, Pricing & Treated Populations. IQUVIA institute. 2018.

Both assets have similar payor coverage projections

- Coverage: **Highly Likely**
- Restricted to Indication
  - **Possible** approval for off-label use
  - Require Genetic Testing
  - Rebates likely necessary



- Coverage: **Required**
- Protected Class
  - Restricted to Indication
  - **No** approval for off-label use
  - Require Genetic Testing

DUK-032

- Will require **higher rebates** required later in asset lifecycle to maintain market share
- Will **require genetic test** for 1L not currently performed until 2L

UNC-023

- Currently there is **no FDA approved** systemic treatments available for IDH1 mutated disease
- **Unlikely** to be the first IDH1 inhibitor to market

Future Consideration: Value-Based Contracting and Medicare Drug Price Negotiation

*Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer. National Cancer Institute

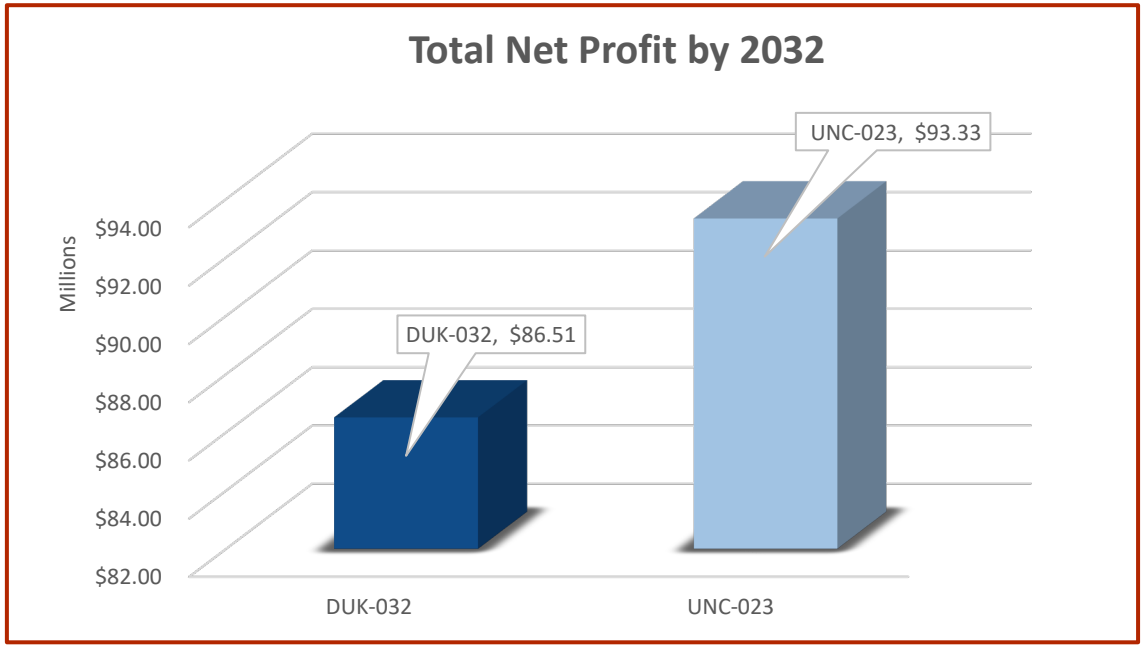
DUK-032 and UNC-023 have similar and favorable regulatory and payor trajectory

	Market size	Competition	Regulatory
DUK-032	✗	✗	✓
UNC-023	✓	✓	✓

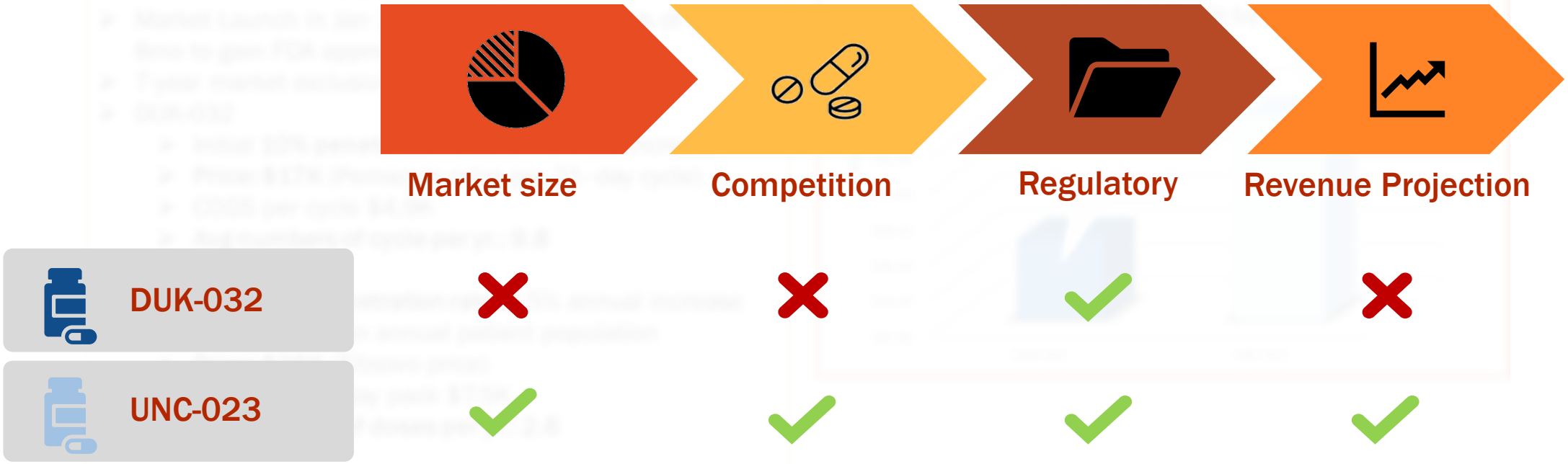
UNC-023 will generate higher total net profit

Model Assumption

- Market Launch in Jan 2026 (Avg. Phase 3 trials of 4yrs + 8mo to gain FDA approval)
- 7-year market exclusivity for Orphan Drug status
- DUK-032
  - Initial **10% penetration rate**, 2% annual increase
  - **Price: $17K** (Pemazyre price per 21- day cycle)
  - COGS per cycle $4.9K
  - **Avg numbers of cycle per yr.: 9.8**
- UNC-023
  - Initial **40% penetration rate**, 2.5% annual increase
  - **10% increase** in annual patient population
  - **Price: $26K** (Tibsovo price)
  - COGS per 30-day pack $7.5K
  - **Avg numbers of doses per yr.: 2.6**



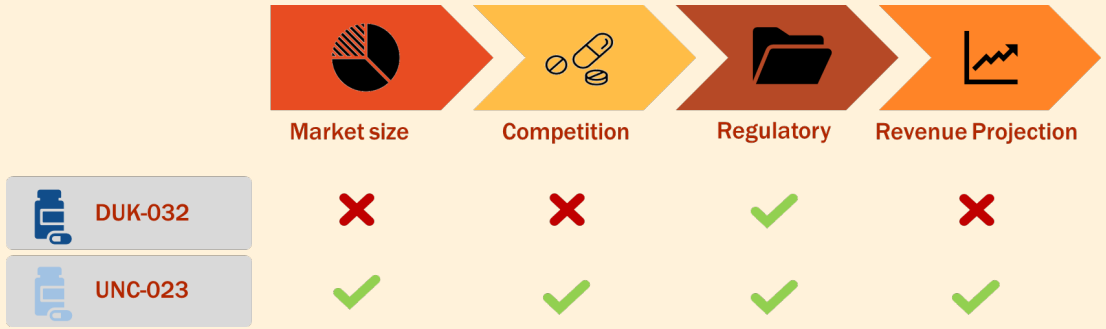
UNC-023 offers the largest commercial opportunity



Recommendation

NCBB Pharma should acquire

UNC-023

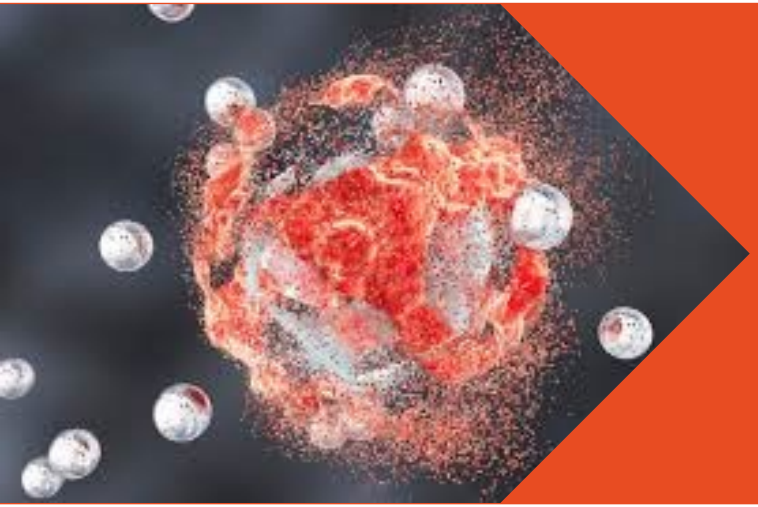


Risks

- UNC-023 clinical data does not provide a clinical advantage over competition and market share is not captured.
- Political climate and the potential to go towards single payor insurance and drug price negotiation

Next Steps

- File for orphan drug status indication
- Pricing and Market Access strategy
- Research global BTC market opportunities (multi-national company)
- Co-indication exploration



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APPENDIX

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Assumptions

DUK-032 Pro-forma financial statement

UNC-023 Pro-forma financial statement

Biliary Tract Cancer Market Sizing resources

Disease Background and Competitive Analysis resources

TKI FGFR1-3 Inhibitors Competitive Analysis

IDH1 Inhibitors Competitive Analysis

Regulatory and Payor Environment Analysis Resources

Assumptions

Market Sizing

- All patients diagnosed with BTC will be treated.
- The historical trends in BTC diagnosis rates hold for the next 20 years.
- Adoption rates are based on market competition: 10% adoption rate for DUK-032 and 40% adoption rate for UNC-023
- Prevalence values from the literature for FGFR and IDH1 genetic mutations are accurate.

Regulations

- Both assets gain FDA approval
- Orphan Drug Status for both assets granting 7-year market exclusivity.

Revenue Projections

- See page 14,20,21 for details

Competitive Landscape

- Current competitive landscape favors UNC-023
- UNC-023 has a less crowded pipeline and is expected to maintain a high market share in the next 5 years

DUK-032 Pro-forma Financial Statement

DUK-032						1	2	3	4	5	6	7
	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
Revenue												
Price	0	0	0	0	0	$ 17,000.00	$ 17,000.00	$ 17,000.00	$ 17,000.00	$ 17,000.00	$ 17,000.00	$ 17,000.00
Penetration Rate						10%	12%	14%	16%	18%	20%	22%
Patient Subgroup						580	580	580	580	580	580	580
Customer Base						58	69.6	81.2	92.8	104.4	116	127.6
Average # of treatments/yr						9.857142857	9.857142857	9.857142857	9.857142857	9.857142857	9.857142857	9.857142857
Total Revenue						$ 9,719,142.86	$ 11,662,971.43	$ 13,606,800.00	$ 15,550,628.57	$ 17,494,457.14	$ 19,438,285.71	$ 21,382,114.29
Costs												
R&D						$ 22,000,000.00	$ -	$ -	$ -	$ -		
COGS per dose						$ 4,935.00	$ 4,935.00	$ 4,935.00	$ 4,935.00	$ 4,935.00	$ 4,935.00	$ 4,935.00
Average # of treatments/yr						9.857142857	9.857142857	9.857142857	9.857142857	9.857142857	9.857142857	9.857142857
COGS per treatment course						$48,645.00	$48,645.00	$48,645.00	$48,645.00	$48,645.00	$48,645.00	$48,645.00
Total Costs						$ 22,048,645.00	$ 48,645.00	$ 48,645.00	$ 48,645.00	$ 48,645.00	$ 48,645.00	$ 48,645.00
Profit						$ (12,329,502.14)	$ 11,614,326.43	$ 13,558,155.00	$ 15,501,983.57	$ 17,445,812.14	$ 19,389,640.71	$ 21,333,469.29

Assumptions:

Price: $17,000 (per Pemazyre price: price per dose of 21-day cycle)
Penetration rate: 10% first year, 2% annual increase
Avg # of cycles/yr.: 9.8 based on Pemazyre' s clinical trials (reference)
R&D cost: total of $22M for phase 3 trials (reference)
Cost of goods sold (COGS) include
- Manufacturing: $5/pk (reference)
- Marketing and Sale: $0.19 for every dollar of price (reference)
- Discount rate for payors: 10% of price

Cost breakdown

	DUK-032	UNC-023
Price	$ 17,000.00	$ 26,115.00
Small molecule COGS (per pack)	$ 5.00	$ 5.00
Marketing and Sale (19 cents/$1)	$ 0.19	$ 0.19
Total marketing and sale/dose	$ 3,230.00	$ 4,961.85
Discount Rate	10%	10%
Discount Amount	$ 1,700.00	$ 2,611.50
Total COGS/dose	$ 4,935.00	$ 7,578.35
Avg numbers of treatments	9.857142857	$ 2,611.50
Total COGS per treatment course	$ 48,645.00	$ 19,790,861.03

UNC-023 Pro-forma Financial Statement

UNC-023						1	2	3	4	5	6	7
	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
Revenue												
Price	0	0	0	0	0	$ 26,115.00	$ 26,115.00	$ 26,115.00	$ 26,115.00	$ 26,115.00	$ 26,115.00	$ 26,115.00
Penetration Rate						40.00%	42.50%	45.00%	47.50%	50.00%	52.50%	55.00%
Patient Subgroup						370	407	447.7	492.47	541.717	595.8887	655.47757
Customer Base						148	172.975	201.465	233.92325	270.8585	312.9	360.5126635
Average # of treatments/yr						2.6	2.6	2.6	2.6	2.6	2.6	2.6
Total Revenue						$ 10,049,052.00	$ 11,744,829.53	$ 13,679,272.04	$ 15,883,154.75	$ 18,391,021.29	$ 21,245,597.10	$ 24,478,449.34
Costs												
R&D						$ 22,000,000.00	$ -	$ -	$ -	$ -	$ -	$ -
COGS per dose						$ 7,578.35	$ 7,578.35	$ 7,578.35	$ 7,578.35	$ 7,578.35	$ 7,578.35	$ 7,578.35
Average # of treatments/yr						2.6	2.6	2.6	2.6	2.6	2.6	2.6
COGS per treatment course						$ 19,703.71	$ 19,703.71	$ 19,703.71	$ 19,703.71	$ 19,703.71	$ 19,703.71	$ 19,703.71
Total Costs						$ 22,019,703.71	$ 19,703.71	$ 19,703.71	$ 19,703.71	$ 19,703.71	$ 19,703.71	$ 19,703.71
Profit						$ (11,970,651.71)	$ 11,725,125.82	$ 13,659,568.33	$ 15,863,451.04	$ 18,371,317.58	$ 21,225,893.39	$ 24,458,745.63

Assumptions:

Price: $26,115 (per Tibsovo price: price per 30-day supply)

Penetration rate: 40% first year, 2.5% annual increase

Patient subgroup increases 10% annually due to trend in prevalence of Cholangiocarcinoma

Avg # of doses per yr. based on Ivosidenib's clinical trials (reference)

R&D cost: total of $22M for phase 3 trials (reference)

Cost of goods sold (COGS) include

- Manufacturing: $5/pk (reference)
- Marketing and Sale: $0.19 for every dollar of price (reference)
- Discount rate for payors: 10% of price

Cost breakdown

	DUK-032	UNC-023
Price	$ 17,000.00	$ 26,115.00
Small molecule COGS (per pack)	$ 5.00	$ 5.00
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Avg numbers of treatments	9.857142857	$ 2,611.50
Total COGS per treatment course	$ 48,645.00	$ 19,790,861.03

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Biliary Tract Cancer Market Sizing Resources:

Title of Article	Indication	Prevalence	Study Methodology	Link to Resource
Gallbladder cancer: Epidemiology, risk factors, clinical features, and diagnosis (UpToDate, 2021)	Gallbladder cancer	Fewer than 5000 new cases are diagnosed each year in the US; In the United States, GBC is the most common cancer arising in the biliary tract [1]. Estimates from the Surveillance, Epidemiology, and End Results (SEER) database reveal an incidence of 1 to 2 cases per 100,000 population in the United States; Despite the increased risk of GBC in patients with gallstones, the overall incidence of GBC in patients with cholelithiasis is only 0.5 percent [25]. Gallstones are present in 70-90% of patients with GBC and a history of gallstones is the largest risk factor for GBC	Review of literature. All topics updated as new evidence becomes available and the peer review process is complete. Literature review current through Feb 2021. The topic last updated Oct 28, 2020.	UpToDate: https://www-uptodate-com.libproxy.lib.unc.edu/contents/gallbladder-cancer-epidemiology-risk-factors-clinical-features-and-diagnosis?search=gallbladder%20carcinoma&source=search_result&selectedTitle=1~76&usage_type=default&display_rank=1
Epidemiology of Gallbladder Disease: Cholelithiasis and Cancer (Stinton, 2012)	Cholelithiasis (gallstones) & GBC	Gallstones constitute a significant health problem in developed societies, affecting 10% to 15% of the adult population; Gallbladder cancer is rare in developed countries. In the U.S., it only accounts for 0.5% of all gastrointestinal malignancies, accounting for less than 5,000 cases per year (1.5 per 100,000)	Review of the epidemiological studies and resources pertaining to diseases of the gallbladder	https://www-ncbi-nlm-nih-gov.libproxy.lib.unc.edu/pmc/articles/PMC3343155/
Epidemiology, pathogenesis, and classification of cholangiocarcinoma (UpToDate, 2021)	Cholangiocarcinoma	The reported incidence of iCC in the United States is one or two cases per 100,000 population. In the United States, an estimated 42,230 primary liver and intrahepatic bile duct cancers are diagnosed annually [10]. Data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program suggest that approximately 15 percent of these are intrahepatic cholangiocarcinoma; Approximately 11,980 cases of extrahepatic biliary tract cancers are diagnosed annually in the United States [10], two-thirds of which are gallbladder cancers. The remainder, approximately 3000 cases per year, are extrahepatic cholangiocarcinomas.	Review of literature. All topics updated as new evidence becomes available and the peer review process is complete. Literature review current through Feb 2021. The topic last updated Feb 15, 2021.	UpToDate: https://www-uptodate-com.libproxy.lib.unc.edu/contents/epidemiology-pathogenesis-and-classification-of-cholangiocarcinoma?search=Cholangiocarcinoma&source=search_result&selectedTitle=4~149&usage_type=default&display_rank=4
Cancer Statistics, 2021 (Siegel, 2021)	Cancer	Reference ten in the Cholangiocarcinoma UpToDate article	Each year, the American Cancer Society estimates the numbers of new cancer cases and deaths in the United States and compiles the most recent data on population-based cancer occurrence. Incidence data (through 2017) were collected by the Surveillance, Epidemiology, and End Results Program; the National Program of Cancer Registries; and the North American Association of Central Cancer Registries.	https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21654
Frequent mutation of isocitrate dehydrogenase (IDH)1 and IDH2 in cholangiocarcinoma identified through broad-based tumor genotyping. (Borger, 2012)	BTC	Mutations in the gene encoding isocitrate dehydrogenase 1 (IDH1) have been identified in 25 percent of intrahepatic cholangiocarcinoma and not extrahepatic cholangiocarcinomas or gallbladder carcinomas	A total of 287 tumors from gastrointestinal cancer patients (biliary tract, colorectal, gastroesophageal, liver, pancreatic, and small intestine carcinoma) were tested during routine clinical evaluation for 130 site-specific mutations within 15 cancer genes. Mutations were identified within a number of genes, including KRAS (35%), TP53 (22%), PIK3CA (10%), BRAF (7%), APC (6%), NRAS (3%), AKT1 (1%), CTNNB1 (1%), and PTEN (1%).	https://pubmed-ncbi-nlm-nih-gov.libproxy.lib.unc.edu/22180306/
Biliary Tract Cancer: Epidemiology, Radiotherapy, and Molecular Profiling (Bridgewater, 2016)	BTC	Incidence of cholangiocarcinoma is 1.67 in 100,000 in the US; Incidence of gall bladder cancer is 1.5 per 100,000 in the US; Table that had all the molecular genomic alterations listed in the next reference found in this reference (referenced the next study)	Review of the epidemiological studies and resources pertaining to biliary tract cancer	https://ascopubs.org/doi/full/10.1200/EDBK_160831
Multigene mutational profiling of cholangiocarcinomas identifies actionable molecular subgroups (Simbolo, 2014)	BTC, molecular profiling	See table from powerpoint	DNA from 412 intrahepatic cholangiocarcinomas, 57 extrahepatic cholangiocarcinomas, and 85 gallbladder cancers were extracted, and next-generation sequencing (NGS) was performed on these specimens. Genomic profiling encompassed 182 cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer.	https://www-ncbi-nlm-nih-gov.libproxy.lib.unc.edu/pmc/articles/PMC4058049/
Biliary tract cancers: SEOM clinical guidelines (Benavides, 2015)	BTC	See table from powerpoint	Review of the resources relevant to biliary tract cancer; Clinical guides in oncology	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4689747/pdf/12094_2015_Article_1436.pdf

Disease background and Competitive Analysis Resources

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2. Golub D, Iyengar N, Dogra S, et al. Mutant Isocitrate Dehydrogenase Inhibitors as Targeted Cancer Therapeutics. *Front Oncol*. 2019;9:417. Published 2019 May 17. doi:10.3389/fonc.2019.00417
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TKI FGFR1-3 Inhibitors Competitive Analysis

	Infigratinib	Pemigatinib***	Derazantinib	Debio1347	Futibatinib	Erdafitinib
Phase/On Market	Phase 3 trial for first line vs SOC (gemcitabine + cisplatin) in tx of pt with unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions/translocations	Currently on market and indicated for tx of adult pts with previously treated unresectable, locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement. (However, currently in a phase III trial for first line vs SOC – FIGHT-302)	Phase II in pretreated	Phase II in pretreated	Phase III for 1st line vs SOC Not yet recruiting	Phase 1 pretreated Phase IIa only Asian patients pretreated
MOA	Selectively binds to FGFR2 mutated cholangiocarcinoma	Selective inhibitor of FGFR1-3	MKI w/ pan FGFR activity	Selective FGFR1-3 inhibitor	Selective irreversible FGFR1-4 inhibitor	Pan FGFR inhibitor
Route of Admin.	Oral	Oral	Oral	Oral	Oral	Oral
Frequency	Once daily (3 weeks on, 1 week off)	Once daily (2 weeks on, 1 week off)				
Line	1st line treatment	2nd line tx / 1st line	2nd line	2nd line	1st line	2nd line
PFS						
SE Profile		Most frequent is hyperK (, others include arthralgias, stomatitis, hyponatremia, abdominal pain, fatigue, dry eyes.				
More info	Requires molecular testing, currently studied in ≥ 18 yo	Requires molecular testing	Requires molecular testing	Requires molecular testing	Requires molecular testing	Requires molecular testing

IDH1 Inhibitors Competitive Analysis

	Ivosidenib	Enasidenib	IDH305	FT 2102	BAY1436032
Phase/On Market	Phase III trial vs placebo (pts were pre-treated with SOC prior)	Not yet studied in cholangiocarcinoma	Phase I	Phase 1/2	Phase 1
MOA	Small molecule inhibitor of mutant IDH1	Small molecule inhibitor of mutant IDH2	Small molecule inhibitor of mutant IDH1	Small molecule inhibitor of mutant IDH1	Small molecule inhibitor of mutant IDH1
Route of Admin.	Oral	Oral	Oral	Oral	Oral
Frequency	Once daily (continuous 28-day cycles)				
Line	2nd line				
PFS/OS	Median PFS was 2.7 months (1.4 mo placebo)/ median OS was 10.3 mo (7.5 mo placebo)				
SE Profile	Most common: ascites, anemia, and increased blood bilirubin, N/V, diarrhea, fatigue, cough, abdominal pain				
Cost	~$1000/day				
More info	The company is requesting Priority Review be granted for the NDA Ivosidenib achieved a 63% reduction in the risk of progression or death in pt with IDH1 mutant cholangiocarcinoma compared with placebo. If approved, it will be the first FDA approved systemic therapy in this setting.				

Regulatory and Payor Environment Analysis Resources

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