Zacks Small-Cap Research

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Critical Outcome Technologies (V.COT-TSX, COTQF-OTC)

V.COT: Zacks Company Report

COT: Unique CHEMSAS™ technology for drug discovery and development; Lead candidate COTI-2 entered clinic—initiating with Buy

Current Price (05/19/16)	$0.54
Valuation	**$1.00**

OUTLOOK

COTI is a clinical stage biopharmaceutical Company. The Company's CHEMSAS® platform technology utilizes a series of predictive computer models to identify potential drug candidates. This technology greatly shortens the timeframe of drug discovery with a high probability of success, therefore saving a great deal of money and increasing revenue potential.

Its lead candidate COTI-2 has entered into the clinic recently with a potential to target multiple cancers.

We are optimistic about the prospects of the Company.

SUMMARY DATA

52-Week High	**$0.38**
52-Week Low	**$0.20**
One-Year Return (%)	**50%**
Beta	**-0.03**
Average Daily Volume (sh)	**78,615**
Shares Outstanding (mil)	**127**
Market Capitalization ($mil)	**$38**
52-Week High	**$0.38**
Institutional Ownership (%)	**3.2**
Insider Ownership (%)	**16.1**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**Small-Growth**
Industry	**Med Products**
Zacks Rank in Industry	**N/A**

ZACKS ESTIMATES

Revenue
(in millions of C$)

	Q1 (Jul)	Q2 (Oct)	Q3 (Jan)	Q4 (Apr)	Year (Apr)
2015	0.00 A	0.00 A	0.00 A	0.00 A	0.00 A
2016	0.00 A	0.00 A	0.00 A	0.00 E	0.00 E
2017					0.00 E
2018					0.50 E

Earnings per Share
(EPS is operating earnings before non recurring items)

	Q1 (Jul)	Q2 (Oct)	Q3 (Jan)	Q4 (Apr)	Year (Apr)
2015	-$0.01 A	-$0.01 A	-$0.01 A	-$0.01 A	-$0.03 E
2016	-$0.01 A	-$0.01 A	-$0.00 A	-$0.01 E	-$0.03 E
2017					-$0.04 E
2018					-$0.04 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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WHAT'S NEW

Update on Fiscal Third Quarter Financials

On March 11, 2016, COTI reported its financial and operating results for the fiscal third quarter ended January 31, 2016.

There was no revenue for the fiscal third quarter.

S&M expenses increased by $40,558 for the quarter as a ramp up in business development activities was reflected in higher professional fees and related travel costs.

G&A expenses decreased $109,069 in the quarter primarily related to lower professional fees and molecule amortization.

R&D expenses increased $51,073 for the quarter primarily reflecting costs related to COTI-2 including; the completion of the IND approval from the FDA, the planning and commencement of the Phase I trial, the continued development costs for new COTI-2 cancer indications, and the preclinical development costs for the clinical candidate successor to COTI-2.

Net loss for the quarter was $637,176 ($0.01 per share), compared to a net loss of $949,503 ($0.01 per share) for the third quarter a year earlier.

Balance Sheet Boosted by New Financings

On **March 17**, 2016, COTI announced that it realized gross proceeds of $1,447,125 upon the exercise of 4,823,750 common share purchase warrants that would otherwise have expired on March 15, 2016. The warrants exercised were part of a private placement financing previously announced in March and April 2011 that resulted in the issuance of common share purchase warrants exercisable at $0.30 per common share.

On March 30, 2016, COTI announced the completion of a non□brokered private placement of 4,841,102 units at a price of CAD $0.30 per Unit for gross proceeds of USD $1.1 million (or approximately CAD $1.4 million) with a successful U.S. life science investor.

Each Unit consists of one common share and one half warrant of the Company. Each whole warrant is exercisable for one common share of the Company at an exercise price of CAD $0.38 per share for a period of 24 months from the date of issue.

On May 2, 2016, COTI announced that it realized gross proceeds of $992,990 and issued 3,598,250 common shares upon exercise of the warrants issued in a private placement financing that closed on April 30, 2014.

We are pleased to see that COTI secured these new financings, which not only boost the company's balance sheet, but more importantly validate the company's technology and preclinical and clinical programs.

As of Jan 31, 2016, COTI had a $1.75 million in cash and investments. With proceeds from the new financings, current cash balance could carry the company's operations into the end of calendar 2016 according to our financial model.

Update on the Phase I Study of COTI-2 for Gynecological Cancers

At the end of 2015, COTI, together with its collaborator MD Anderson, initiated a **Phase I** clinical trial to evaluate COTI-2 for the treatment of patients with **gynecological cancers** including ovarian cancer, fallopian tube cancer, endometrial cancer, cervical cancer, and peritoneal cancer (NCT02433626).

This Phase I trial is a single arm, single center, open-label study of COTI-2 in female patients with platinum-resistant, recurrent ovarian (including fallopian tube or primary peritoneal cancer), endometrial, or cervical cancer. COTI-2 will be self-administered as a single agent, orally, once daily for 5 days followed by 2 treatment-free days each week. 1 cycle will be defined as 4 weeks of treatment as described (5 days on, 2 days off per week). Participants will remain on treatment until they experience a lack of benefit.

The primary endpoints will be safety and tolerability. Secondary endpoints include clinical response and progression free survival (PFS). The trial will enroll up to **46 patients**.

Treatment of the first cohort commenced on **February 15**, 2016.

The company commenced treating patients in the second cohort on **April 19**, 2016. Treatment of the second cohort will continue to evaluate COTI□2's safety profile at a dosage level twice that of the first cohort. Prior to initiating cohort two, the independent Dose Escalation Committee reviewed the safety data from all patients in the first cohort and unanimously approved moving to dosing the next cohort.

We expect top line data to be available **in 1H2017**.

COTI is also planning clinical trials in Canada and the US for the treatment of patients with recurrent **head and neck** squamous cell cancer. The Company will file an Investigational New Drug application with the US FDA and is also completing a Clinical Trial Application for submission to Health Canada.

The next step with COTI-2 will be the initiation of a **Phase II** trial for **ovarian cancer** in 2017 following the conclusion of the Phase I trial. The logic of choosing ovarian cancer is because as many as 95% of ovarian cancer patients have a p53 gene mutation, and the market for ovarian cancer treatment in the US will well surpass $1 billion.

COTI-2 received an **orphan-drug designation** for ovarian cancer by the FDA in June 2014.

Update on ROSALIND Technology

Overview

Critical Outcome Technologies Inc. (COT.V) is a clinical stage biopharmaceutical Company which is focused on the discovery and development of cancer treatments through targeted therapeutics.

The Company has developed a proprietary artificial intelligence platform, **CHEMSAS®**, which utilizes a series of predictive computer models to identify compounds with a high probability of being successfully developed from disease specific drug discovery through chemical optimization and preclinical testing.

In addition to CHEMSAS®, COTI has also developed ROSALIND. **ROSALIND** is a computer platform for realizing the promise of personalized medicine for cancer patients. The goal of ROSALIND is to provide better personalized treatment options based on the genetic profile of the patient's cancer.

ROSALIND is a dynamic, programmable computer simulation of how cell signaling pathways are altered by specific gene mutations that are associated with specific types of cancers. The technology produces a comprehensive mathematical model of cell signaling and identifies optimal personalized cancer treatment options.

While access to high-quality cancer gene mutation profiling continues to evolve, **personalized cancer therapy** is really a big data problem. For example, the number of unique single, double, and triple drug combinations from just 150 cancer drugs would be in excess of 540,000. This is simply too many potential therapies for any physician or group of physicians to evaluate. ROSALIND addresses this big data problem.

The technology uses a gene expression and mutation profile of a patient's tumor to evaluate a full range of available therapies. ROSALIND V2.0 can analyze more than 1000 gene mutations simultaneously.

ROSALIND targets the multi-billion dollar personalized cancer **gene profiling market**. The Company is seeking commercial and validation development partners.

The Launch of ROSALIND Could Generate Revenue Soon

On March 14, 2016, COTI announced the launch of ROSALIND™.

The launch here means that the technology is available for use / testing by physicians – for them to try it out; see how it works and can work for them.

The use of the technology is being offered without a fee at this time to provide feedback on its use and for COTI to refine the service based upon this feedback. Part of this launch strategy is to get oncologists excited by the use and value the technology can bring them that will allow the Company to turn it in to a pay for use service.

Following validation it is likely that patients will pay for the service/information initially like they now pay for the gene expression profile. The longer term plan would be to have the ROSALIND report paid for by insurance companies/third party payer.

ROSALIND has successfully undergone initial validation but now requires further real world testing. Assessments suggesting optimal personalized drug treatment options are immediately available for physicians to order free of charge during this validation phase. In a recent system stress test, ROSALIND evaluated 1.4 million drug combinations and provided multiple potential treatment options for patients in less than 90 minutes.

We believe ROSALIND will empower physicians to make efficient individual patient treatment decisions based on an individual's cancer gene mutation and expression profile. The services could begin generating meaningful revenue for COTI **in 2017**.

We continue to be Bullish on COTI Shares

We are optimistic about the prospect of Critical Outcome Technologies (COTI). We raise our fair value of the company to CAD$1.00 per share from previous CAD$0.75 per share based on recent achievements the company has made.

COTI is a clinical-stage biopharmaceutical company with a current focus on cancer. Over the years, the Company has developed a unique, proprietary drug discovery platform technology **CHEMSAS®**. This is the core value for the Company and differentiates the Company from other biotech companies in our view.

The CHEMSAS® platform has the advantages of dramatically shortening the timeframe of drug discovery with an increase in the probability of success, therefore saving millions of dollars in R&D costs and increasing the revenue potential of successful candidates.

Base on this CHEMSAS® platform, COTI has built a pipeline with a focus on cancer and other unmet medical needs. The Company's lead drug candidate **COTI-2** is a small molecule discovered using the

CHEMSAS® technology. COTI-2 has a unique mechanism of action which not only restores p53 functions to a wide range of common p53 mutations but also negatively modulates the PI3K/AKT/mTOR pathway and as well inhibits cancer stem cells (CSC).

In preclinical studies, COTI-2 has demonstrated strong anti-cancer efficacy in different cancer types and a favorable safety profile. Currently COTI-2 is in a **Phase I** clinical study in patients with advanced or recurrent gynecologic malignancies including **ovarian cancer**.

In addition to COTI-2, the Company also has numerous other drug candidates in different discovery and development stages targeting different cancers including colon and AML as well as other programs including MRSA, multiple sclerosis, Alzheimer's, and HIV.

With respect to valuation, we think the current market price does not reflect the Company's true value. Currently, the Company's shares are trading at about CAD$0.50 per share, which values the Company at CAD$69 million in market capitalization. We think this undervalues the Company based on what we have discussed above.

We agree that it's always difficult to exactly value a development stage biotech Company. We don't think a DCF model is appropriate for the valuation of COTI since even the Company's lead candidate COTI-2 is still a few years away from reaching the market. Instead, one better way is to use relative value metrics to reach fair value for COTI. According to our experience and current market conditions, most small cap biotech companies are valued at from $50 million to $2 billion in market cap based on how advanced the Company's pipeline is and the market potential of the Company's drug candidates. Other factors affecting a small cap biotech valuation include cash balance, burn rate and management expertise and experience.

Our price target of CAD$1.00 per share values COTI at CAD$130 million in market cap, which we think is very conservative.

Data is the ultimate driving force of a biotech Company. We believe when more data are generated from the Company's lead candidate, COTI-2, and from other early stage candidates, value will also be generated for the Company and its shareholders. In this regard, we will keep a close eye on the Company's development plan and update investors on any new data (either clinical or preclinical) generated from its drug candidates.

We are also pleased to see that the Company is seeking collaboration opportunities for its **ROSALIND** technology. If successful, the collaboration could boosts the Company's balance sheet in a non-dilutive way.

But keep in mind **the risks**. As we discussed, COTI is still a clinical stage biopharmaceutical company. Our valuation assumes the final approval of lead candidate COTI-2 and other candidates. In order for the candidates to reach the market, the Company still needs to overcome both clinical and regulatory hurdles which have proven to be high.

Cash burn is another concern. When COTI-2 enters into the clinic, we expect R&D expenses will also increase. As of Jan 31, 2016, COTI held $1.75 million in cash, which, plus funds raised in recent financings, can only support the Company's operations into the calendar 4th quarter of 2016 according to our financial model. We expect the Company needs to tap the capital market for new funding on a regular basis. We reminder investors that equity financing will dilute the existing shareholder base, and could cause the share price to fall.

But generally speaking, we think the stock has a typical high risk/high return profile, which could be appropriate for investors with a high risk tolerance and relatively long investment horizon.

OVERVIEW

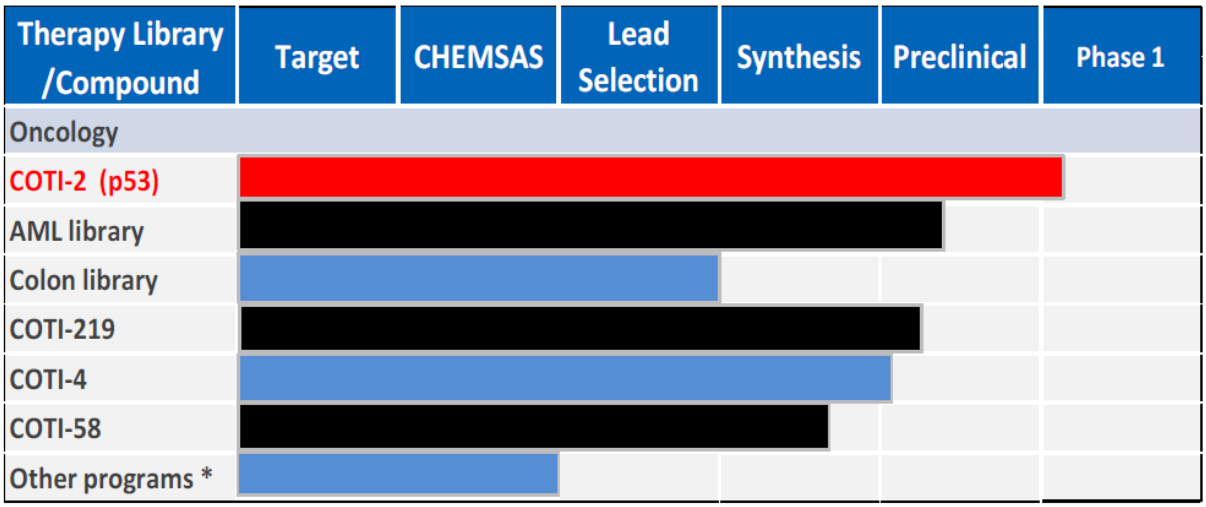
Critical Outcome Technologies Inc. (COT.V) is a **clinical stage** biopharmaceutical Company which is focused on the discovery and development of **cancer treatments** through targeted therapeutics.



The Company has developed a proprietary artificial intelligence platform, **CHEMSAS®**, which utilizes a series of predictive computer models to identify compounds with a high probability of being successfully developed from disease specific drug discovery through chemical optimization and preclinical testing.

The CHEMSAS® platform technology is focused on small molecules, and as a drug candidate discovery engine can be applied to any disease target with a modest amount of information for the target of interest. The CHEMSAS® technology uses machine learning to rapidly develop targeted therapies thereby dramatically reducing the timeline and cost of getting new drug therapies to market.

Based on the CHEMSAS® technology, COTI has built a robust pipeline with focus on cancer therapy. The Company's lead compound, **COTI-2**, has a novel p53-dependent mechanism of action with selective and potent anti-cancer activity. COTI-2 entered into a human clinical **Phase I** trial near the end of 2015. COTI is developing COTI-2 for **gynecologic cancers**, including ovarian, cervical, and endometrial. The Company is also developing drug candidates for the treatment of acute myelogenous leukemia, colorectal cancer, small cell lung cancer, MRSA, multiple sclerosis, Alzheimer's disease, and HIV.



Other programs for MRSA, Multiple Sclerosis, Alzheimer's, and HIV Integrase

Critical Outcome Technologies Inc. was originally founded as a private company in 1999 and is based in London, Canada. The Company went to public in 2006 and its shares are listed on the TSX Venture Exchange under the trading symbol of COT.V and in the United States on the OTCQB under the trading symbol of COTQF.

INVESTMENT THESES

The Unique CHEMSAS® Drug Discovery and Development Technology

Over the years, COTI has developed a unique, proprietary platform technology, **CHEMSAS®** (Computerized Hybrid Expert Molecular Structure Activity Screening), a machine learning (artificial intelligence, AI) based drug discovery and development platform technology.

CHEMSAS®® is a multi-staged computational platform technology based upon a hybrid of machine learning technologies and proprietary algorithms that allow accurate predictions of biological activity from the molecular structure.



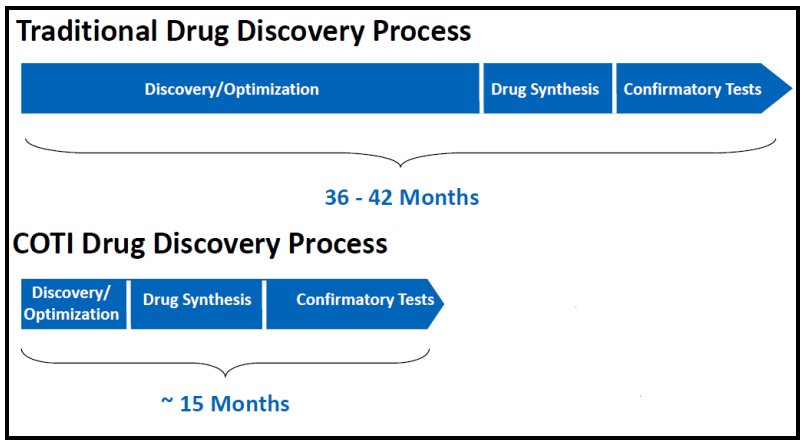
In order to accurately predict the biological activity of a molecule, the series of proprietary algorithms are applied to complex 3D molecular structures of the molecule to produce unique 2D data patterns composed of more than 250 descriptors. These unique 2D molecular data patterns are then used to develop hybrid predictive models relating molecular structure to specific target biological properties that traditionally require expensive and time consuming in vitro or in vivo tests. The final lead candidates are selected based on an optimal profile of probable physical chemical, biological, efficacy and ADMET properties.

To ensure that CHEMSAS® remains a cutting edge technology, new and updated prediction models are being constantly added and refined. New molecules are continuously being added to the database and new in silico versions of tests and assays are also being developed in order to make CHEMSAS® predictive capability as comprehensive as possible.

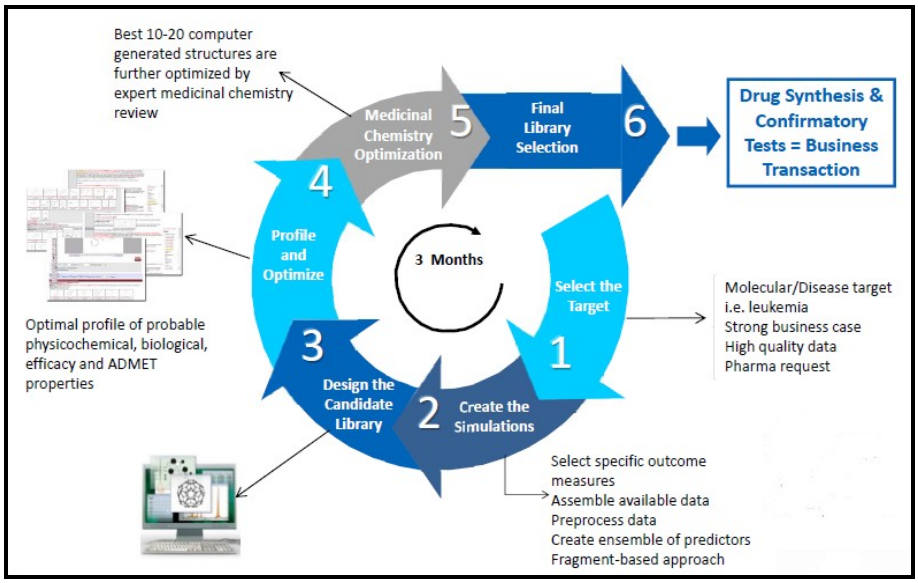
CHEMSAS® has **competitive advantages** over traditional drug discovery methods.

- First, CHEMSAS® can **accelerate** identification of drug candidates. This faster time to market saves millions of dollars for drug discovery and development and yields increased profits for each successful new drug by providing a longer revenue period under the patent life.
- In addition to time savings, this rigorous scientific screening process allows customers to fill their pipelines with drug candidates that have a **higher probability** of clinical success.

CHEMSAS® drug discovery process only takes about 15 months from discovery/optimization, while traditional drug discovery processes can take 36-42 months.



COTI's discovery/optimization takes only about 3 months to establish a final library of 6-10 promising candidates. A summary of the process is set out in the graphic below.

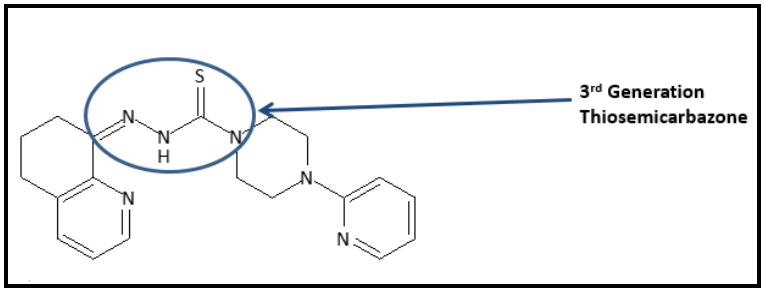


Using this methodology, COTI can establish a 1st generation compound library of 1000-1500 structures in about 2-3 months. Then, a 2nd generation library undergoes final computational profiling leading to a **final library** of 6-10 potential leads. After the final leads are selected, COTI will conduct a patent search on the most promising candidates to establish composition of matter patentability. After the lead candidates are selected, the Company will license or develop the most promising ones into preclinical and clinical studies.

The end results are a shortened period of time and higher probability of success for the drug discovery and development phase which can save millions of dollars and increase the revenue period under patent protection and minimize regulatory risk. Further, this platform is designed to repeatedly identify high probability compounds and quickly build a pipeline targeting multiple unmet medical needs.

COT-2: A Novel Activator of p53 Targeting Multiple Cancers

COTI-2 is a novel small molecule discovered using the Company's CHEMSAS®® discovery engine. COTI-2 is a 3rd generation **thiosemicarbazone** engineered for low toxicity and designed as an **oral treatment** of susceptible cancers.



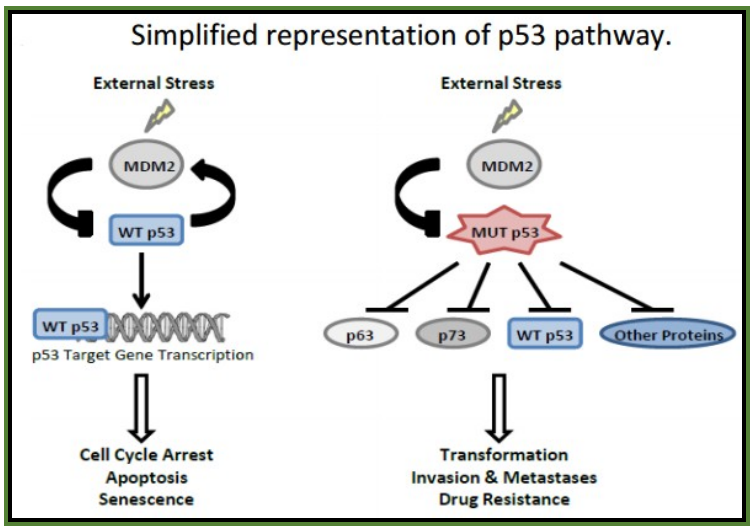
COTI-2 restores **p53 function** to a wide range of common p53 mutations and also acts as a negative modulator of the **PI3K/AKT/mTOR** pathway.

Background of the p53 Pathway

p53 is a multifunctional **tumor suppressor protein** that regulates many important cellular responses, such as cell growth arrest and apoptosis, to environmental/external stress. p53 is encoded by the TP53 gene in humans and has been widely regarded as possibly holding a key to the future of cancer therapies.

In response to cellular stress, wild-type p53 induces cell cycle arrest and/or apoptotic cell death. p53 is regulated primarily by ubiquitin ligase **MDM2**, which binds to p53 and activates downstream anti-cancer gene expression which kills cancer cells by promoting cell cycle arrest, apoptosis and senescence.

Mutant p53 protein is the single most important cancer causing gene mutation known, is often found at high levels in more than 50% of human cancers and contributes to the transformation of cancer cells, metastasis and drug resistance. Mutations not only disable the p53 tumor suppressive function but also exhibit cancer-promoting activity by gaining oncogenic properties. Mutant p53 is an array of mutant proteins with oncogenic properties that varies among patients. Reactivation of wild type p53 to restart apoptosis is an effective way to kill cancer cells.

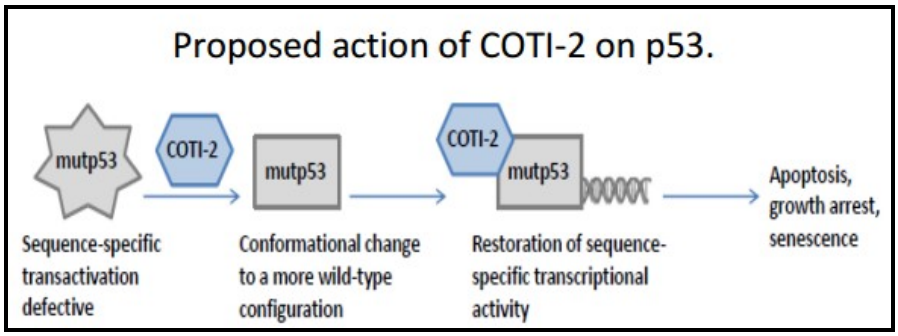


COTI-2 is a Potent Activator of Mutant p53

Data indicates that COTI-2 normalizes mutant p53 to wild-type-like conformation to promote apoptosis/cell death. The mechanism is most likely through zinc chelation by COTI-2's thiosemicarbazone core structure.

Metal ion chelation has been shown to induce p53 conformational changes. Wild-type p53 binds zinc and requires it for proper function. Mutant p53 is relatively unable to bind zinc.

Metal chelation by a thiosemicarbazone is hypothesized to provide a source of zinc that allows for a p53 mutant conformation change. Thiosemicarbazones induce a wild-type-like conformational change in the p53 mutant protein that restores sequence-specific p53 transcription.



Research has shown that COTI-2 activity is strongly correlated with p53 status. A bioinformatics analysis of the NCI molecular targets database demonstrated that low COTI-2 IC_{50} was strongly associated with the presence of any p53 mutation, and that low COTI-2 IC_{50} was also strongly associated with the presence of p53 hotspot mutations occurring at amino acids 175, 248, and 273.

	LOW IC_{50} (<250 nM)	HIGH IC_{50} (≥ 250 nM)	TOTAL
ANY p53 MUTATIONS	30	0	30
p53 WILDTYPE	5	5	10
TOTAL	35	5	N = 40 cell lines
	LOW IC_{50} (<250 nM)	HIGH IC_{50} (≥ 250 nM)	TOTAL
HOTSPOT p53 MUTATIONS	13	0	13
p53 WILDTYPE	5	5	10
TOTAL	18	5	N = 23 cell lines

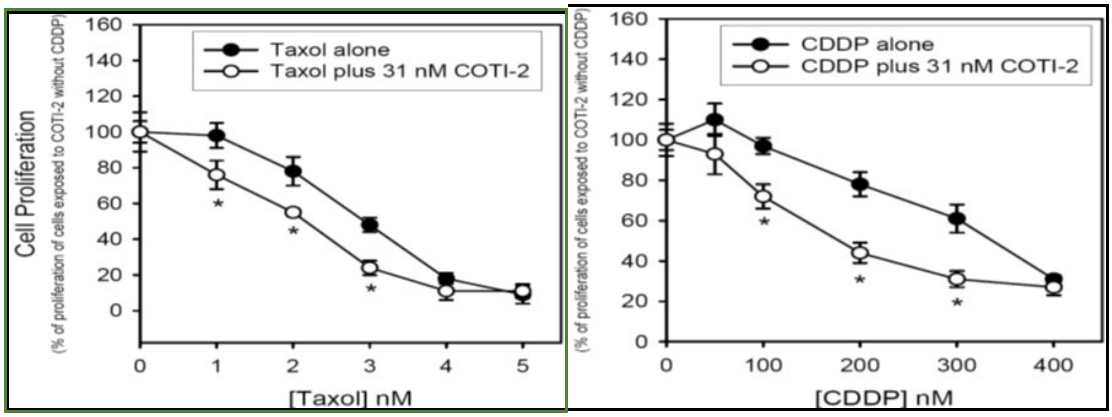
Extensive **preclinical studies** demonstrated COTI-2's ability to restore mutant p53 function and thus induce cancer cell death in many common p53 mutations. COTI-2 has demonstrated nanomolar activity in vitro and in vivo as a **single agent** against multiple cancer cell lines from various cancer types including small cell lung, non-small cell lung, colon, brain, ovarian, endometrial, triple negative breast, head and neck, and pancreatic.

COTI-2 is more efficacious relative to standard chemotherapeutic agents in many cell types. In preclinical cell line studies, COTI-2 exhibited more potent activity against human brain cancer cell lines than temozolomide, cisplatin (Platinol®), and BCNU. COTI-2 was also more potent than Gleevec® (Imatinib mesylate) in lung cancer cells.

TUMOR TYPE	CELL LINE	COTI-2 IC_{50} (nM)	GLEEVEC® IC_{50} (nM)
SCLC	DMS-114	51.0	15,733.0
	DMS-153	73.0	14,041.0
	SHP-77	156.0	18,835.0
NSCLC	H226	15,000.0	72,000.0
	A460	7,900.0	81,000.0
	A549	6,300.0	53,000.0

TUMOR TYPE	CELL LINE	COTI-2 IC_{50} (nM)	TEMZOLOMIDE IC_{50} (nM)	CISPLATIN IC_{50} (nM)	BCNU® IC_{50} (nM)
GLIOMA	U87	48.0	≥100,000.0	490.0	1,520.0
	SNB-19	8.0	≥100,000.0	870.0	2,250.0
	SF-268	66.0	≥100,000.0	ND	ND
	SF-295	184.0	≥100,000.0	ND	ND

In combination studies, COTI-2 enhanced the activity of standard chemotherapeutic agents including Taxol, Cisplatin, Tarceva, and Erbitux. In DMS114 SCLC cells, COTI-2 in combination with either Taxol or Cisplatin (CDDP®) had a greater-than-additive effect (indicated by differences between data points at each concentration) where indicated by asterisks. Similar results were obtained with Carboplatin.



In human colon cell lines, COTI-2 enhanced the effectiveness of Erbitux® regardless of KRAS status.

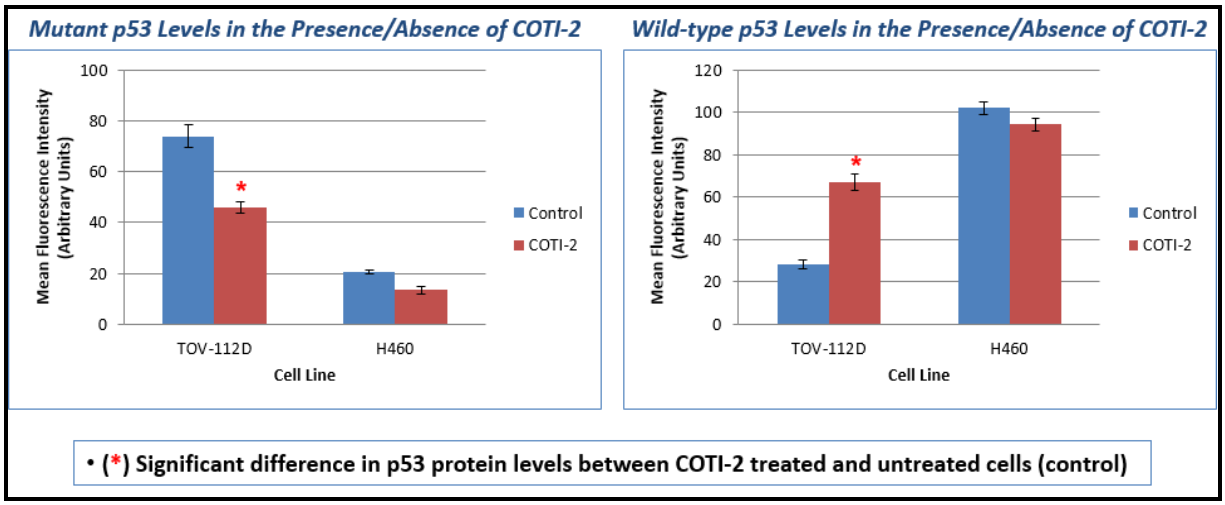
CELL LINE	TISSUE TYPE	EGFR/KRAS STATUS	COTI-2 IC_{50} (nM)	COTI-2 + ERBITUX® (nM)	ERBITUX® IC_{50} (mg/ml)	CI at IC_{50}
HT-29	COLON	KRAS-WT	200.0	6.4	>0.1	<1.0 (Synergism)
COLO-205	COLON	KRAS-WT	4.7	3.0	>0.1	<1.0 (Synergism)
HCT-15	COLON	KRAS-MUT	8.3	4.0	>0.1	<1.0 (Synergism)
HCT-116	COLON	KRAS-MUT	3.6	4.1	>0.1	<1.0 (Synergism)
SW620	COLON	KRAS-MUT	165.0	82.0	>0.1	<1.0 (Synergism)

Mean IC_{50} for COTI-2, Erbitux®, and combinations

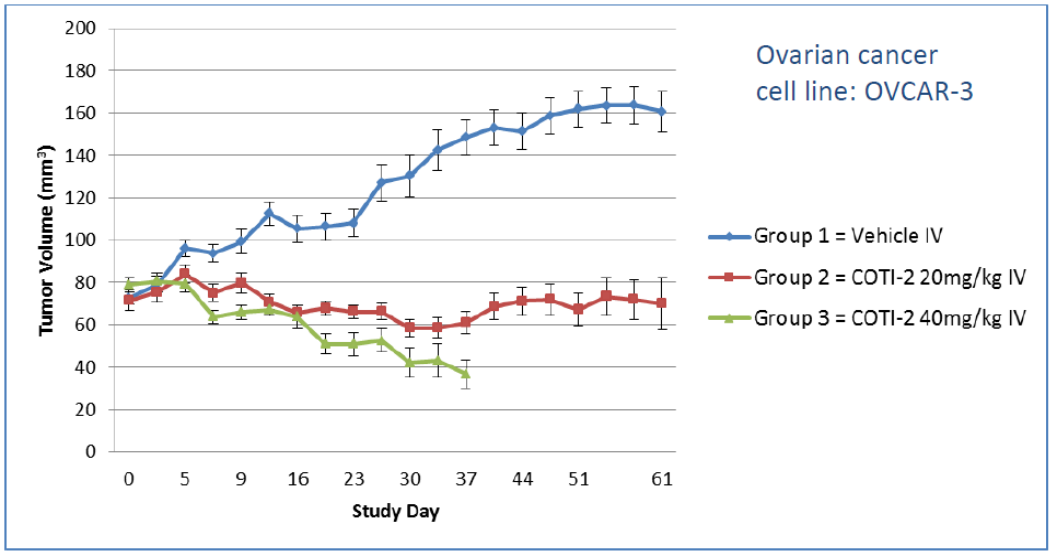
CI < 1.0 (Synergism) CI = 1.0 (Additive) CI > 1.0 (Antagonism)

Studies also showed that, COTI-2 induced no significant **resistance** or **cross-resistance** in SCLC cell lines (DMS-114 and SHP-77). Drug resistance remains one of the most pressing problems in the management of cancer patients. In this regard, COTI-2 may provide physicians an alternative to many existing cancer treatment regimes.

COTI-2 significantly reduced p53 mutant protein levels and significantly increased wild-type p53 protein levels in TOV-112D **ovarian cells** likely by inducing a conformational change. While COTI-2 had no significant effect on p53 protein levels in the H460 non-small cell lung cancer cell line, which does not carry the mutant p53 protein.



In a preclinical study using OVCAR-3 **ovarian cancer cell line**, COTI-2 significantly reduced tumor volume in a dose dependent manner.



Multiple in vivo xenograft models indicate that COTI-2 does not exhibit any overt signs of **toxicity**. Available PK data suggests that COTI-2 can be administered orally once daily or less. Blood levels of COTI-2 following single oral dose maintained >> IC_{50} for more than 48 hours.

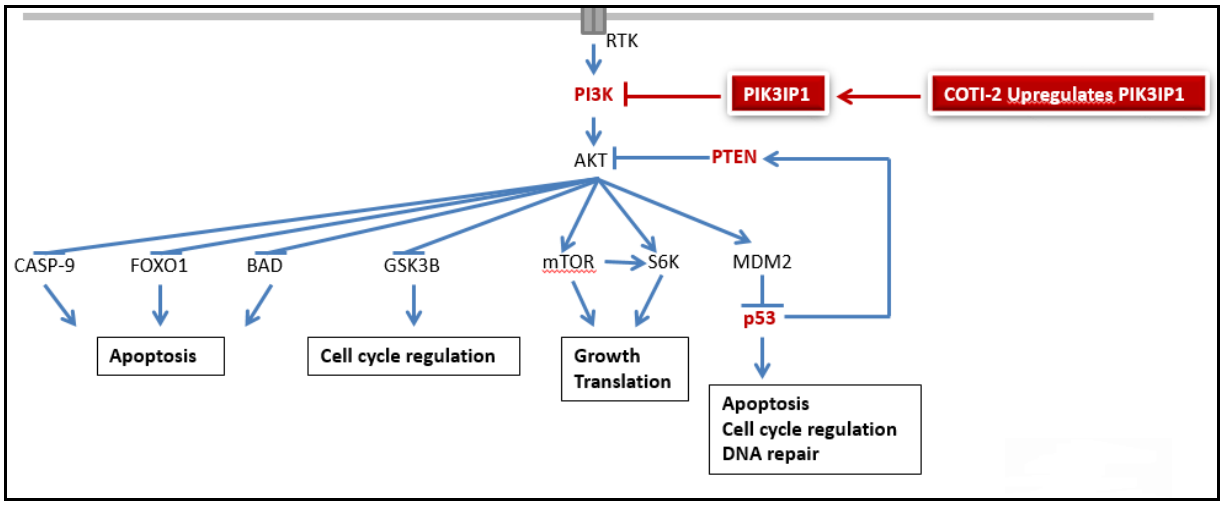
COTI-2 Also Targets the PI3K/AKT/mTOR Pathway and Cancer Stem Cells

The PI3K/AKT/mTOR pathway

COTI-2 is not a traditional kinase inhibitor, but it has been shown to **negatively modulate** the PI3K/AKT/mTOR pathway.

The PI3K/AKT/mTOR signaling pathway is involved in cell proliferation, survival, motility, and metabolism. Abnormalities or mutations in this pathway are typically found in many cancerous cells, which lead to tumor proliferation, survival, metastasis, and drug resistance. Frequent activation of the PI3K/AKT/mTOR pathway has been reported in a broad range of human cancers at frequencies of up to 50%.
COTI-2 **negatively modulates** the PI3K/AKT/mTOR pathway to target cell growth and proliferation.

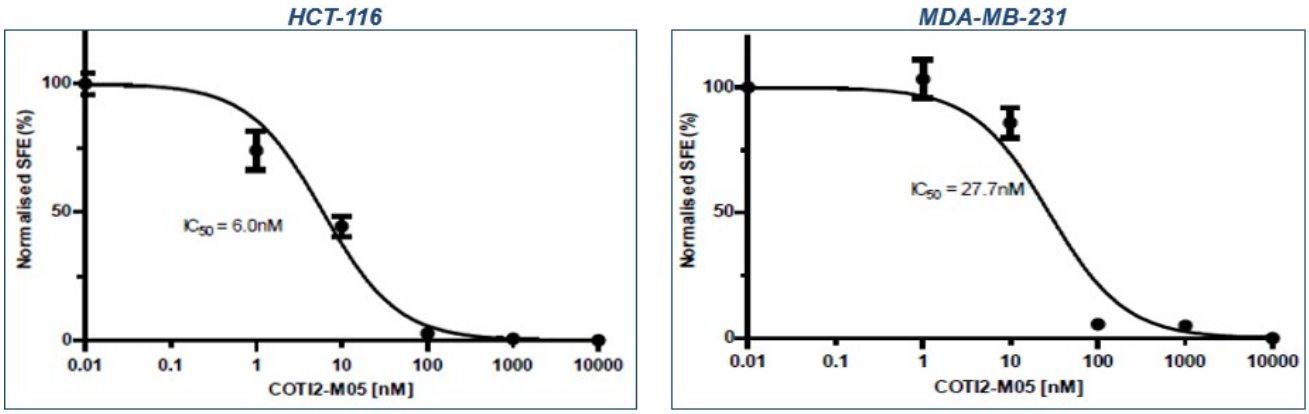
- COTI-2 directly inhibits PI3K via the upregulation of PIK3IP1,
- Increased/restored p53 function stimulates PTEN activity,
- Increased PTEN activity leads to AKT protein degradation.



The end results are increased apoptosis, cell cycle regulation and DNA repair of the cancer cells.

Cancer Stem Cell Inhibition

In a preclinical cell line experiment, COTI-2 inhibited both MDA-MB-231 (IC_{50} = 27.7 nM) and HCT-116 (IC_{50} = 6.0 nM) cancer stem cells as determined by a stem cell sphere assay. The positive control, DAPT, exhibited an IC_{50} = 50 μM.



The Advantages of COTI-2

COTI-2 is being developed as an **oral treatment** for solid tumors; it is easy to synthesize (3 steps). COTI□2's specific protein target, low toxicity, combination effectiveness with standard agents, and potential for longer term outpatient therapy as an oral agent, supports a dramatic change in the treatment of susceptible cancers.

COTI-2 is a 3rd generation thiosemicarbazone that demonstrates both class and unique effects. **The class effects** include restoration of p53 function to a wide range of common p53 mutations and binding/chelation of 2^+ metal ions (zinc, copper, and/or iron).

The unique effects include **negative modulation of the PI3K/AKT/mTOR pathway** and cancer stem cell (CSC) inhibition.

When compared to similar competitors currently under development, COTI-2 has a big advantage in efficacy. COTI-2 is the most potent activator of mutant p53 with IC50's in the low nanomolar range in multiple human cancer cell lines. While Kevetrin is active at greater than 100 micromolar level, and APR-246 is active only at a high micromolar range.

DRUG	COTI-2	Kevetrin	APR-246 / PRIMA-1^{MET}
COMPANY	Critical Outcome Technologies Inc.	Cellceutix Corp	Aprea
MECHANISM OF ACTION	Targets mutant p53 (restoration of wild-type p53 conformation and activity)	Targets wild-type and mutant p53 (MDM2-related mechanism)	Targets mutant p53 (restoration of wild-type p53 conformation and activity)
IN VITRO EFFICACY	Most potent (nanomolar range of activity)	Least potent (activity >100 µM)	Much less potent than COTI-2 (activity in high micromolar range)
CLINICAL PHASE OF DEVELOPMENT	Phase 1	Phase 1	Phase 1/2
INDICATIONS	Gynecological malignancies (first patient in January 2016)	Solid tumors (ongoing)	Hematological malignancies and prostate cancer (phase 1/2 completed)

Ovarian Cancer and the Market

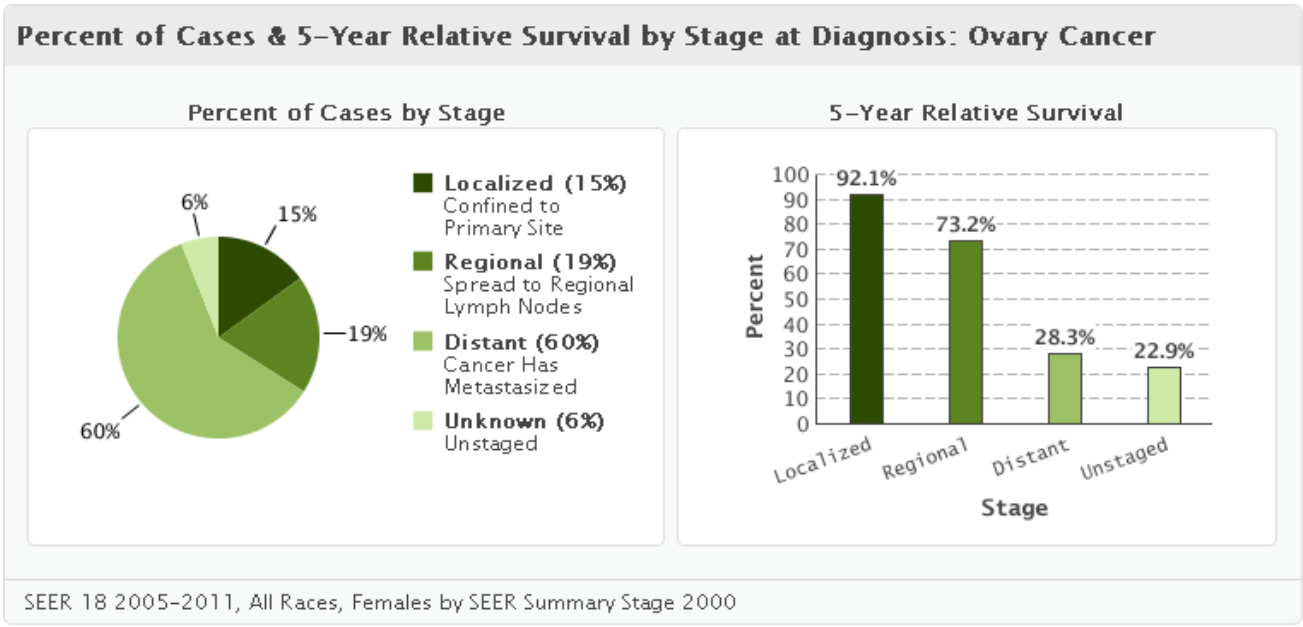
Ovarian Cancer

According to the American Cancer Society, **ovarian cancer** accounts for about 3% of cancers among women. In 2015, it is estimated that about 21,290 women received a new diagnosis of ovarian cancer and about 14,180 women died from ovarian cancer in the US.

Ovarian cancer ranks fifth in cancer deaths among women, but accounts for more deaths than any other cancer of the female reproductive system. This cancer mainly develops in older women. About half of the women who are diagnosed with ovarian cancer are 63 years or older.

About 90 percent of ovarian cancers are **epithelial tumors,** derived from the epithelium, the thin layer of tissue that covers the ovaries. Other ovarian cancers include **Germ cell carcinoma tumors, Stromal carcinoma tumors,** and **Small cell carcinoma of the ovary.**

Survival rates differ for different stage of ovarian cancers. For all types of ovarian cancer, the 5-year relative survival is 45%. If ovarian cancer is found (and treated) before the cancer has spread outside the ovary (localized), the 5-year relative survival rate is 92%. However, only 15% of all ovarian cancers are found at this early stage. 5-year survival rate for metastasized cancer is only 28.3%.



Treatment of Ovarian Cancer

The main treatments for ovarian cancer include surgery, radiation, chemo, hormone and targeted therapy.

The standard **chemo therapy** is the **combination** of a platinum compound, such as cisplatin or carboplatin, and a taxane, such as paclitaxel (Taxol®) or docetaxel (Taxotere®).

Some of the other common chemo drugs that are helpful in treating ovarian cancer include Abraxane, Xeloda, Topotecan, Vinorelbine, and Melphalan.

There are two **targeted therapies** approved by the FDA for the treatment of ovarian cancer: Bevacizumab (Avastin®) and Olaparib (Lynparza™).

Avastin (marketed by Roche) belongs to a class of drugs known as **angiogenesis inhibitors**. In clinical studies, avastin has been shown to shrink or slow the growth of advanced epithelial ovarian cancers. Trials to see if bevacizumab works even better when given along with chemotherapy have shown good results in terms of shrinking tumors, but it doesn't seem to help women live longer.

Olaparib (marketed by AstraZeneca) is the first oral prescription medicine used to treat patients with *BRCA*-mutated advanced ovarian cancer who have received three or more prior chemotherapy medicines. The efficacy of Olaparib was investigated in a single-arm study in patients with deleterious germline BRCA-mutated advanced ovarian cancer. Efficacy results are summarized in the following table.

	N=137
Objective Response Rate (95% CI)	34% (26, 42)
Complete Response	2%
Partial Response	32%
Median DOR in months (95% CI)	7.9 (5.6, 9.6)

Hormone therapy is rarely used to treat epithelial ovarian cancer, but is more often used to treat ovarian stromal tumors. Two common types of hormone therapy are Tamoxifen and aromatase inhibitors including letrozole (Femara®), anastrozole (Arimidex®), and exemestane (Aromasin®).

The Ovarian Cancer Drug Market and COTI-2 Opportunity

The world market for ovarian cancer treatments has been dominated by generic chemotherapies following patent expiries for leading drugs almost 15 years ago. However, the market has seen new approvals in recent years, such as Avastin, Lynparza, and Yondelis (approved in the EU, but not in the US) which are gradually capturing market share.

The industry is changing, and novel therapies are in development. However, the success of these agents will depend on how much of an improvement they provide over the current standard of care. This is particularly of importance for cost-effectiveness assessments, which are having a greater impact on the industry as healthcare budgets are tightened. With a growing incidence of ovarian cancer and high recurrence and mortality rates, the demand for better treatment will continue to bolster this drug market.

Multiple sources have projected that the market for ovarian cancer treatment will **well surpass $1 billion** in the next few years. According to a new report by visiongain the overall world market for drugs treating cancer of the ovaries will reach $1.71 billion in 2019. Decision Resources, one of the world's leading research and advisory firms for pharmaceutical and healthcare issues, also projects that the ovarian cancer drug market will more than triple over the next decade, increasing from $460 million in 2011 to $1.4 billion in 2021 in the United States, France, Germany, Italy, Spain, the United Kingdom and Japan.

We think the market growth will be primarily driven by the penetration of newly approved therapies and new approvals in the following years. Market growth will also be driven by the growing patient population and rising costs of drug therapies.

COTI-2 is a new class of targeted anti-ovarian cancer agent, which has a different mechanism of action compared to Avastin and Lynparza, two targeted agents currently marketed in the US. COTI-2 targets both the p53 path way and the PI3K/AKT/mTOR pathway as well as cancer stem cell inhibition. COTI-2's potent anti-cancer efficacy and favorable safety profile as well as its oral formulation may positon it as the choice of targeted therapy for ovarian cancer patients if it finally reaches the market.

Licensing Opportunities

One value driver for COTI is the potential for licensing opportunities. The Company is actively pursuing licensing opportunities during the development of COTI-2 consistent with its strategy to be a pipeline provider to major pharmaceutical companies and has been approached by potential partners for its lead candidate COTI-2. Our guess is that after a positive readout of the Phase I trial, licensing opportunities could materialize.

More importantly, positive data from COTI-2 will validate the CHEMSAS® technology, which could lead to more licensing opportunities for COTI-2 and for the technology.

Licensing deals are important to COTI. First, these deals will provide revenue and hence **non-dilutive** funding for the Company's operations. Secondly, any licensing deal is a validation of the Company's technology and clinical programs. Thirdly, these licensing deals will accelerate the development of COTI's other preclinical and clinical programs.

Other Technologies

In addition to CHEMSAS®, COTI has also developed ROSALIND. **ROSALIND** is a computer platform for realizing the promise of personalized medicine for cancer patients. The goal of ROSALIND is to provide better personalized treatment options based on the genetic profile of the patient's cancer.

ROSALIND is a dynamic, programmable computer simulation of how cell signaling pathways are altered by specific gene mutations that are associated with specific types of cancers. The technology produces a

comprehensive mathematical model of cell signaling and identifies optimal personalized cancer treatment options.

While access to high-quality cancer gene mutation profiling continues to evolve, **personalized cancer therapy** is really a big data problem. For example, the number of unique single, double, and triple drug combinations from just 150 cancer drugs would be in excess of 540,000. This is simply too many potential therapies for any physician or group of physicians to evaluate. ROSALIND addresses this big data problem.

The technology uses a gene expression and mutation profile of a patient's tumor to evaluate a full range of available therapies. ROSALIND V2.0 can analyze more than 1000 gene mutations simultaneously.

ROSALIND targets the multi-billion dollar personalized cancer **gene profiling market**. The Company is seeking commercial and validation development partners.

INCOME STATEMENT

	2015 (Apr)					2016 (Apr)					2017 (Apr)	2018 (Apr)	2019 (Apr)	2020 (Apr)	2021 (Apr)
C$ in million except per share data	Q1	Q2	Q3	Q4	FYE	Q1	Q2	Q3	Q4	FYE	FYE	FYE	FYE	FYE	FYE
Grant revenue	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
License/Royalties	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.50	$1.50	$3.00	$5.00
Product revenue	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$5.00	$50.00
Total Revenues	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.50**	**$1.50**	**$8.00**	**$55.00**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CoGS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.60	11.00
Gross Income	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.50**	**$1.50**	**$6.40**	**$44.00**
Gross Margin	-	-	-	-	-	-	-	-	-	-	-	100.0%	100.0%	80.0%	80.0%
R&D	$0.23	$0.36	$0.35	$0.42	$1.36	$0.30	$0.35	$0.40	$0.50	$1.54	$2.50	$4.00	$5.50	$7.50	$12.00
% R&D	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SG&A	$0.76	$0.61	$0.66	$0.59	$2.63	$0.61	$0.64	$0.60	$0.72	$2.57	$3.00	$3.50	$5.50	$10.00	$15.00
%SG&A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other Expenses	($0.05)	($0.04)	($0.03)	($0.02)	($0.13)	($0.01)	($0.02)	($0.03)	($0.01)	($0.07)	$0.00	$0.00	$0.00	$0.00	$0.00
Operating Income	**($1.0)**	**($0.9)**	**($1.0)**	**($1.0)**	**($3.9)**	**($0.9)**	**($1.0)**	**($1.0)**	**($1.2)**	**($4.0)**	**($5.5)**	**($7.0)**	**($9.5)**	**($11.1)**	**$17.0**
Operating Margin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	30.91%
Other Net	($0.0)	($0.0)	$0.0	$0.0	$0.0	($0.1)	$0.0	$0.3	$0.1	$0.3	$0.0	$0.0	($0.1)	($0.1)	($0.1)
Pre-Tax Income	**($1.0)**	**($0.9)**	**($0.9)**	**($0.9)**	**($3.8)**	**($1.0)**	**($0.9)**	**($0.6)**	**($1.2)**	**($3.7)**	**($5.5)**	**($7.0)**	**($9.6)**	**($11.2)**	**$16.9**
Income taxes(benefit)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.8
Tax Rate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Reported Net Income	**($1.0)**	**($0.9)**	**($0.9)**	**($0.9)**	**($3.8)**	**($1.0)**	**($0.9)**	**($0.6)**	**($1.2)**	**($3.7)**	**($5.5)**	**($7.0)**	**($9.6)**	**($11.2)**	**$16.1**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Net Margin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diluted Shares Out	103.1	103.8	115.2	151.6	118.4	125.9	126.4	127.9	128.0	127.0	150.0	200.0	250.0	300.0	350.0
Reported EPS	**($0.01)**	**($0.01)**	**($0.01)**	**($0.01)**	**($0.03)**	**($0.01)**	**($0.01)**	**($0.00)**	**($0.01)**	**($0.03)**	**($0.04)**	**($0.04)**	**($0.04)**	**($0.04)**	**$0.05**
One time charge	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*
Non GAAP Net Income	**($1.0)**	**($0.9)**	**($0.9)**	**($0.9)**	**($3.8)**	**($1.0)**	**($0.9)**	**($0.6)**	**($1.2)**	**($3.7)**	**($5.5)**	**($7.0)**	**($9.6)**	**($11.2)**	**$16.1**
Non GAAP EPS	**($0.01)**	**($0.01)**	**($0.01)**	**($0.01)**	**($0.03)**	**($0.01)**	**($0.01)**	**($0.00)**	**($0.01)**	**($0.03)**	**($0.04)**	**($0.04)**	**($0.04)**	**($0.04)**	**$0.05**

Source: Company filings and Zacks estimates

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HISTORICAL ZACKS RECOMMENDATIONS



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