# Clovis Oncology, Inc. (CLVS)

| | |
|---|---|
| Rating | **OUTPERFORM*** |
| Price (04 Jan 12, US$) | 14.03 |
| Target price (US$) | 21.00[1] |
| 52-week price range | 14.27 - 11.70 |
| Market cap. (US$ m) | 291.34 |
| Enterprise value (US$ m) | 156.54 |

*Stock ratings are relative to the relevant country benchmark.
[1]Target price is for 12 months.

INITIATION

## Finding "hENTs" in Treating Pancreatic Cancer

- **We are initiating coverage of Clovis (CLVS) with an Outperform rating and a 12-month target price of $21.** Founded in 2009, Clovis focuses on developing and commercializing oncology drugs. Clovis's management has significant experience from similar previous operations (notably Pharmion).
- **Clovis has three development programs:** (1) CO-101, a lipid-conjugated gemcitabine in PII/III, (2) CO-1686, a selective mutant EGFR inhibitor in PI, and (3) CO-338, a PARP inhibitor in PI/II. An important development commonality among all three compounds is a defined target and/or mechanism of action with a "molecular differentiator and/or twist". Also important in our view, Clovis has adopted a molecular diagnostics strategy to select patients who will likely benefit the most from their treatments.
- **CO-101 could drive a near-term paradigm shift in the treatment of pancreatic cancer (PC).** Survival has not improved in the last 15 years. CO-101 could potentially increase survival in a subset of patients. It is being studied in a PII/III trial in metastatic PC (Data expected in Q4'12). The rationale for developing CO-101 is based on the hENT1 hypothesis: Patients with low hENT1 respond poorly to gemcitabine, the current standard of care.
- **Pipeline projects focus on two of the most interesting mechanisms of action for oncology drugs.** CO-1686 is an oral, small molecule inhibitor of mutant forms of EGFR, including the T790M+ mutant, with potential for use as first- and second-line treatment of NSCLC. Also, CO-1686 could have fewer side effects than Tarceva and Iressa. CO-338 is PARP inhibitor that has delivered promising initial data in PI/II trials.
- **50% Probability in Target Price:** Our TP is derived using a DCF valuation of CO-101 (only), assuming 50% probability of success, U.S. and EU launch in Q1'14, worldwide peak sales of $645M, cash flows through 2021, 10% discount rate, and zero terminal value. If CO-101 is not approved or launched, then there could be a material negative effect on the stock price. A 100% probability of success for CO-101 yields a valuation of $39 per share; the current $14 share price implies a ~30% probability of success.

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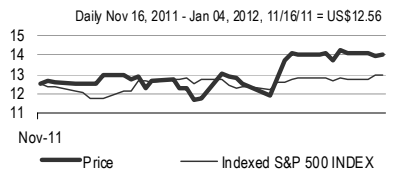
**Share price performance**




*On 01/04/12 the S&P 500 INDEX closed at 1277.3*

| Quarterly EPS | Q1 | Q2 | Q3 | Q4 |
|---|---|---|---|---|
| 2010A | — | — | — | — |
| 2011E | — | — | — | -0.68 |
| 2012E | -0.56 | -0.73 | -0.98 | -1.35 |

**Financial and valuation metrics**

| Year | 12/10A | 12/11E | 12/12E | 12/13E |
|---|---|---|---|---|
| EPS (CS adj.) (US$) | -4.41 | -2.16 | -3.63 | -3.36 |
| Prev. EPS (US$) | — | — | — | — |
| P/E (x) | -3.2 | -6.5 | -3.9 | -4.2 |
| P/E rel. (%) | -21.9 | -52.0 | -33.9 | -40.9 |
| Revenue (US$ m) | — | — | — | — |
| EBITDA (US$ m) | -38.5 | -50.4 | -82.9 | -93.3 |
| OCFPS (US$) | -3.97 | -1.82 | -3.30 | -3.48 |
| P/OCF (x) | — | -7.7 | -4.2 | -4.0 |
| EV/EBITDA (current) | -7.6 | -5.8 | -3.5 | -3.1 |
| Net debt (US$ m) | -11 | -135 | -62 | -116 |
| ROIC (%) | — | -846.96 | 4,329.84 | 4,275.35 |

| | | | |
|---|---|---|---|
| Number of shares (m) | 20.77 | IC (current, US$ m) | 1.58 |
| BV/share (Next Qtr., US$) | — | EV/IC (x) | — |
| Net debt (Next Qtr., US$ m) | — | Dividend (Next Qtr., US$) | — |
| Net debt/tot cap (Next Qtr., %) | -98.8 | Dividend yield (%) | — |

*Source: Company data, Credit Suisse estimates.*

# Executive summary

We are initiating coverage of Clovis with an Outperform rating and a 12-month target price of $21. Our target price is based only on Clovis's lead development candidate, CO-101 (using a 50% probability of success); the rest of the company's pipeline could offer further medium and/or long term potential upside. Clovis's IPO took place in November 2011 at an offer price of $13.

Initiating at Outperform with a 12 month target price of $21

Founded in 2009, Clovis is a biotechnology company focused on the development and commercialization of oncology drugs. Clovis's management team has significant experience from similar previous operations, most notably with Pharmion (which had the same CEO, CFO, CMO and CRO team), which was eventually acquired by Celgene for $2.9B in 2007.

An oncology-focused company with proven and experienced management

Clovis currently has three development programs: (1) CO-101, a lipid-conjugated form of gemcitabine in-licensed from Clavis Pharma in November 2009, is being studied in a pivotal Phase II/III trial. (2) CO-1686, an inhibitor of mutant forms of EGFR in-licensed from Avila Therapeutics in May 2010, will likely be studied in a Phase I trial in H1 2012. (3) CO-338, a PARP inhibitor in-licensed from Pfizer (PF-01367338) in June 2011, is currently being investigated in a Phase I/II trial. Clovis maintains full controlling development and commercialization rights and the majority of the economic value for all in-licensed programs. Clovis plans to commercialize these products in most of the major geographic territories.

3 development projects: CO-101 – potential pivotal trial, CO-1686 – entering PI, CO-338 – In PI/II

All of Clovis's pipeline projects have important development commonalities: all three programs have defined targets and/or mechanisms of actions with a "molecular differentiators and/or twist". Also, importantly in our view, Clovis has adopted a molecular diagnostics strategy for all projects. In our view, companion diagnostics (CDx) will continue to become an increasingly important component of development, approval, and commercial sensitivities for oncology drugs. The recent approval of Pfizer's Xalkori (crizotinib) and Roche's Zelboraf (vermurafenib) are examples. We describe Clovis' specific CDx offering within the relevant sections of this report. We highlight the CDx primer in the appendix of this report adapted from recent work from the Credit Suisse's Life Science Tools and Diagnostics team.

All projects have:

(1) established mechanisms of action with a "molecular differentiators/ twist"

(2) companion diagnostics integrated into development/ commercialization plans

Exhibit 1: **Clovis Pipeline**

## Clovis Pipeline

| | Target Indications | Partners | Current Status | Highlights |
|---|---|---|---|---|
| 1. CO-101 Lipid Conjugated Gemcitabine | ▪ 1st-line metastatic pancreatic cancer with specific biomarker<br>▪ 2nd-line metastatic pancreatic cancer | ▪ Diagnostic developed by Ventana Medical<br>▪ Licensed from Clavis | ▪ Ph 2 pivotal trial is currently underway<br>▪ Data readout in 4Q'12 | ▪ Key near-term valuation driver<br>▪ Potential for better efficacy than Gemcitabine in certain patients |
| 2. CO-1686 EGFR Inhibitor | ▪ 2nd-line EGFR mutated NSCLC<br>▪ 1st-line EGFR mutated NSCLC | ▪ Diagnostic developed by Roche Molecular Systems<br>▪ Licensed from Avila | ▪ Planning to initiate Ph 1/2 trial in 1H'12<br>▪ Data expected in 2H'13 | ▪ No approved drugs for 2nd-line NSCLC<br>▪ Potential to replace Tarceva in 1st-line NSCLC |
| 3. CO-338 PARP Inhibitor | ▪ Breast cancer<br>▪ Ovarian cancer | ▪ Diagnostic partner TBD<br>▪ Licensed from Pfizer | ▪ Ph 1/2<br>▪ Planning to initiate pivotal studies in 2013 | ▪ PARP inhibitors could be next major class of drugs in oncology |

*Source: Clovis*

CO101 is the primary focus for investors. CO-101 is a lipid conjugated form of gemcitabine in a potential pivotal trial (LEAP study) for pancreatic cancer. Data readout due Q4 2012. We model *ca*$645M peak revenues with numerous upside opportunities

The primary near-term focus of investors is CO-101, which is important from an investor's perspective, is due to read out potentially pivotal data this year (company guidance is for Q4 2012) in 1st-line metastatic pancreatic cancer (mPC). We conservatively model peak worldwide peak revenues for CO-101 of *ca*$645M (in 2021). CO-101 is a lipid-conjugated form of gemcitabine. The scientific rationale and hypothesis for developing CO-101 is relatively simple and the clinical trial program that Clovis is undertaking eloquently tests this hypothesis. The thesis is that gemcitabine principally enters tumor cells via a cell surface transporter called hENT1. However, a significant proportion of the patient population expresses low levels of hENT1. Hence, these hENT-1 low patients have a low/null response to gemcitabine. The lipid-tail of CO-101 can allow the drug to bypass hENT1 to enter tumor cells. Thus, the thesis states that CO-101 is effective in both hENT1 low and high expressing patients. This hypothesis is supported by numerous studies/ observations, most importantly, five studies retrospectively looking at the response of gemcitabine treatment in hENT1 low and high patients. The potential pivotal "The **L**ow h**E**NT1 and **A**denocarcinoma of the **P**ancreas" (LEAP) trial, prospectively tests (1) response of both hENT1 low and high patients to CO-101 – the primary end point being overall survival (2) if response to gemcitabine is dependent on hENT1 expression. LEAP is due to readout in Q4 2012 potentiating a early 2013 launch for CO-101. Our *ca*$645M peak sales estimate for CO-101 is based up the assumption of a *ca*50% penetration in hENT1 low patients (assuming a hENT1 expression level cutoff of 50%) and an average price of *ca*$25K/pa. We see modest competition for CO-101 in PC and particularly note that almost all other PC drugs in development are being tested in combination with gemcitabine and do not test the hENT1 hypothesis. We highlight further incremental upside for CO-101 in 2nd line pancreatic cancer and other solid tumors such as breast and ovarian.

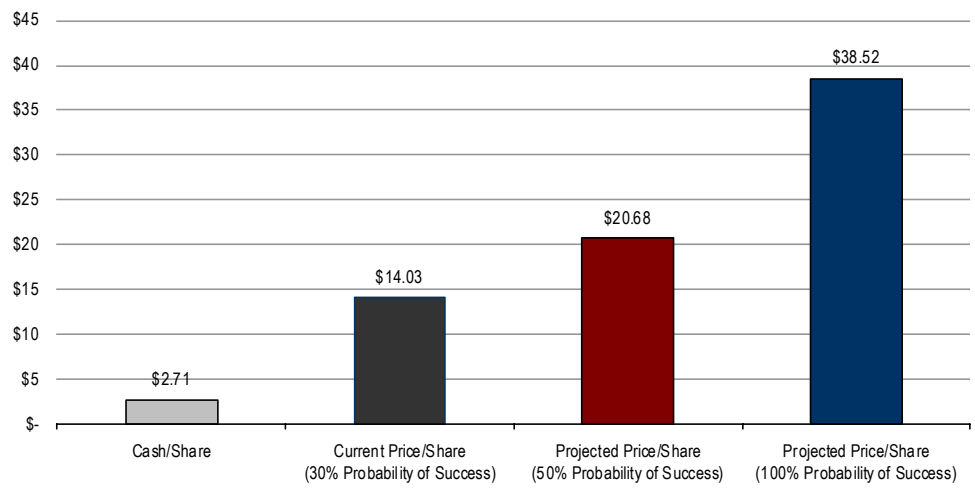
Turning to the other two development projects, both CO-1686 and CO-338 are early stage projects, but focus arguably on the two most interesting mechanisms of actions for oncology drugs. Clovis is developing CO-1686, a oral small molecule inhibitor of mutant forms of EGFR, including the T790M+ mutation. Thus CO-1686 has the potential for the treatment of both first and second-line NSCLC patients and demonstrate less side effects than established TKI's (Tarceva and Iressa). Clovis has an accelerated development pathway for CO-1686, with the potential for IND to NDA in ~4 years – 2nd line NSCLC will be the first indication. The Phase I/II trial, intended to show evidence of efficacy in patients with T790M+ NSCLC who failed Tarceva and Iressa, is due to start in Q2 2012. CO-338 is a Poly-ADP ribose protein (PARP) inhibitor that has delivered promising initial phase in PI/II trials. With the recent disappointment of Sanofi's iniparib and AstraZeneca's olaparib, CO-338 is the leading PARP in development.

CO-1686 (EGFR) and CO-338 (PARP) are early in development but are arguably the leading compounds in their respective MOA categories

The $21 target price (TP) is derived using our DCF methodology for valuing early development-stage biotechnology companies. We expect that CO-101 will likely be used in patients with hENT1-low locally advanced and metastatic pancreatic cancers. Our model assumes that CO-101 will launch in the U.S. and EU in Q1 2014 and remain under patent protection until 2021 (We see upside to both of these assumptions). Our model assumes that CO-101 will reach worldwide peak revenues of *ca*$645M at an average price per patient (across the U.S. and EU) of *ca*$25K/pa in 2021. We model revenues for CO-101 coming from the U.S. and major EU countries only. We risk-weight the cash flows with a 50% probability of success for CO-101, and employ a standard 10% discount rate. We assume zero cash flows beyond 2021. Working backwards from the current stock price, a *ca*30% probability of success would yield a *ca*$14 stock price. Our assumptions also include a further $150M equity raise in 2013. Our TP is based on the approval and launch of CO-101 in the U.S. and EU. If these events do not occur, there could be a material negative impact on our TP.

$21 TP based on standard DCF valuation of CO-101 only, assuming a 50% probability of success (and *ca*$645M peak revenues). A 100% probability of success yields a $39 TP and the current *ca*$14 share price implies a *ca*30% probability of success for CO-101

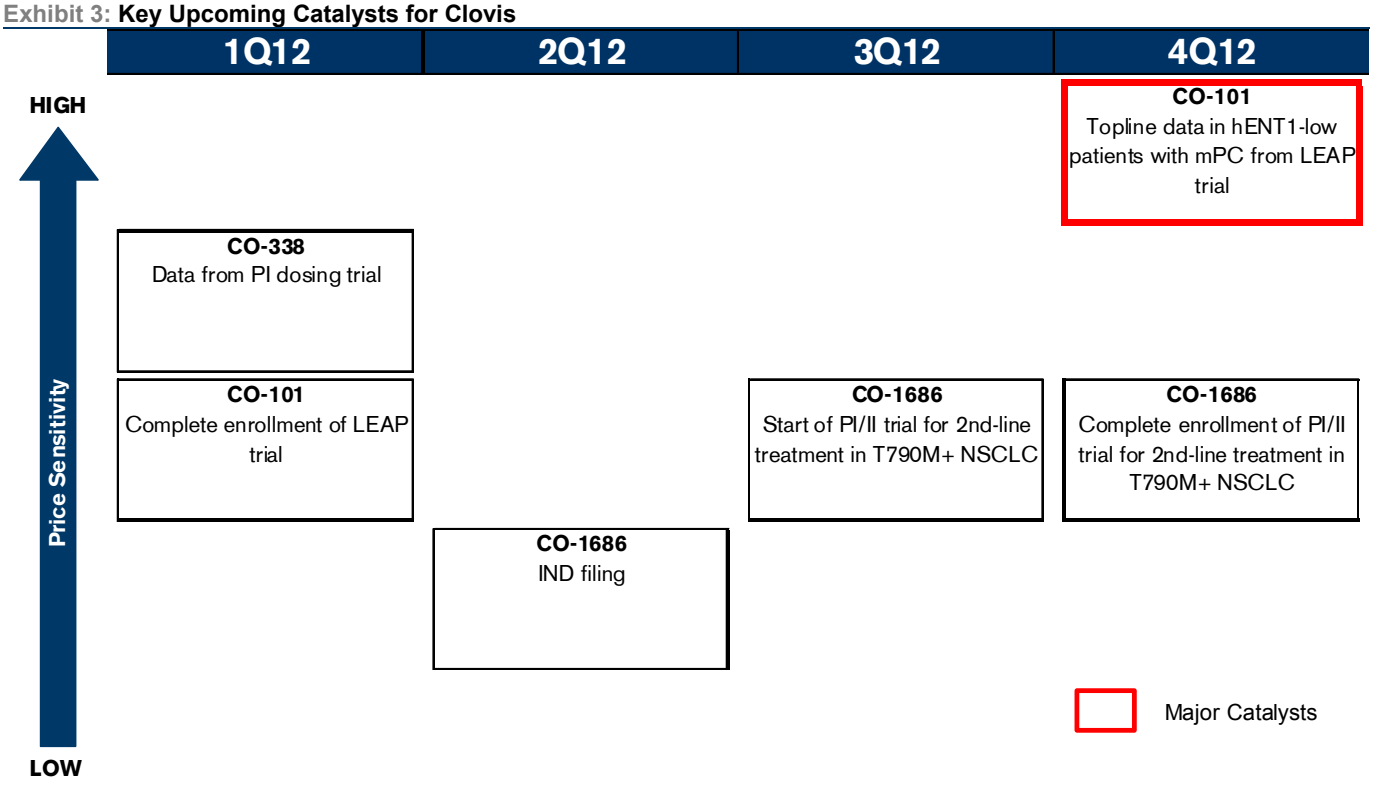
**Exhibit 2: Clovis Valuation (all numbers/share)**




*Source: Clovis, Credit Suisse estimates*

# Timelines

**Exhibit 3: Key Upcoming Catalysts for Clovis**




*Source: Clovis, Credit Suisse analysis*

**Exhibit 4: Clovis P&L Summary**

| *(Dollars in thousands, except share and per share amounts)* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2011E** | **2012E** | **2013E** | **2014E** | **2015E** | **2016E** | **2017E** | **2018E** | **2019E** | **2020E** | **2021E** |
| CO-101 | 0 | 0 | 0 | 97,015 | 182,835 | 273,749 | 369,989 | 471,791 | 565,511 | 615,339 | 643,752 |
| **Revenues:** | **0** | **0** | **0** | **97,015** | **182,835** | **273,749** | **369,989** | **471,791** | **565,511** | **615,339** | **643,752** |
| **COGS** | **0** | **0** | **0** | **9,702** | **18,283** | **27,375** | **36,999** | **47,179** | **56,551** | **61,534** | **64,375** |
| **Gross Profit** | **0** | **0** | **0** | **87,314** | **164,551** | **246,375** | **332,990** | **424,612** | **508,960** | **553,805** | **579,377** |
| **Operating expenses:** | | | | | | | | | | | |
| Research and Development | 36,000 | 53,547 | 60,000 | 65,000 | 45,000 | 41,062 | 36,999 | 37,743 | 33,931 | 30,767 | 32,188 |
| Selling, General, and Administrative | 7,500 | 29,494 | 33,500 | 82,463 | 87,761 | 90,337 | 92,497 | 94,358 | 96,137 | 98,454 | 90,125 |
| Acquired IPRD | 7,000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total Operating Expenses** | **50,500** | **83,040** | **93,500** | **147,463** | **132,761** | **131,400** | **129,496** | **132,101** | **130,068** | **129,221** | **122,313** |
| **Operating Income (Loss)** | **(50,500)** | **(83,040)** | **(93,500)** | **(60,149)** | **31,791** | **114,975** | **203,494** | **292,510** | **378,893** | **424,584** | **457,064** |
| **Net Investment and Interest Income/(Expense)** | **1,529** | **745** | **1,032** | **444** | **478** | **1,300** | **3,230** | **5,580** | **8,635** | **12,071** | **15,765** |
| **Pretax Income (Loss)** | **(48,971)** | **(82,295)** | **(92,468)** | **(59,705)** | **32,269** | **116,275** | **206,724** | **298,090** | **387,528** | **436,655** | **472,829** |
| Provision For Income Taxes | 0 | 0 | 0 | 0 | 0 | 0 | (28,941) | (59,618) | (77,506) | (87,331) | (94,566) |
| *Effective Tax Rate* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *14%* | *20%* | *20%* | *20%* | *20%* |
| **Net Income (Loss)** | **(48,971)** | **(82,295)** | **(92,468)** | **(59,705)** | **32,269** | **116,275** | **177,782** | **238,472** | **310,022** | **349,324** | **378,263** |
| **Basic EPS** | **($2.26)** | **($3.79)** | **($3.48)** | **($1.90)** | **$1.02** | **$3.66** | **$5.57** | **$7.42** | **$9.56** | **$10.66** | **$11.41** |
| **Diluted EPS** | **($2.16)** | **($3.63)** | **($3.36)** | **($1.83)** | **$0.98** | **$3.47** | **$5.22** | **$6.87** | **$8.72** | **$9.55** | **$10.00** |
| Basic Shares Outstanding | 21,664 | 21,701 | 26,582 | 31,481 | 31,604 | 31,753 | 31,936 | 32,158 | 32,430 | 32,761 | 33,165 |
| Diluted Shares Outstanding | 22,664 | 22,702 | 27,531 | 32,639 | 33,017 | 33,477 | 34,039 | 34,724 | 35,560 | 36,580 | 37,824 |

*Source: Clovis, Credit Suisse estimates*

# Risks to our investment thesis

Key risks to our Clovis target price include the following:

- **CO-101 approval.** Our model assumes that CO-101 will be approved and launched in both the U.S. and EU in Q1 2014. If one or the other of these events do not occur, then there would be a material negative effect on the stock price.
- **Readout from LEAP trial.** Our model assumptions are based on expectations that CO-101 will show a statistically significant survival benefit relative to gemcitabine in hENT1-low patients with metastatic pancreatic cancer. If CO-101 is shown to be equally or less efficacious than gemcitabine in prolonging survival in this patient subpopulation, then CO-101 may not be approved or sales of CO-101 may fall short of expectations.
- **Financing risk.** Clovis recently raised net proceeds of $130M in an IPO in November 2011. We expect Clovis will be able to fund operations into early 2013. We are modeling a capital raise (and associated dilution) of $150M in 2013 to fund commercialization of CO-101 in the U.S. and EU. The need for additional capital and/or more than expected dilution would have a negative impact on our valuation.
- **CO-101 launch and sales ramp.** In modeling CO-101, we developed a patient-driven model to attempt to forecast the launch trajectory and peak sales. However, if any of the following parameters are worse than our expectations, our sales estimates for CO-101 could be too high:
    - Pricing
    - Clovis economics
    - Treatment rate
    - Average duration of therapy
    - Emergence of new competing agents

# CO-101 – A new era for pancreatic cancer?

## CO-101 summary

The 101 on CO-101

**CO-101 could drive a near term paradigm shift in the treatment of pancreatic cancer.** CO-101 is the primary focus for investors. CO-101 is a lipid conjugated form of gemcitabine that is in a potential pivotal trial (LEAP study - data readout due Q4 2012) for the treatment of metastatic pancreatic cancer (mPC). CO-101 development rationale is based upon the "hENT1" hypothesis. We estimate a 2014 launch for CO-101 and model *ca*$645M peak revenues in mPC, with numerous further upside opportunities.

## Background to pancreatic cancer

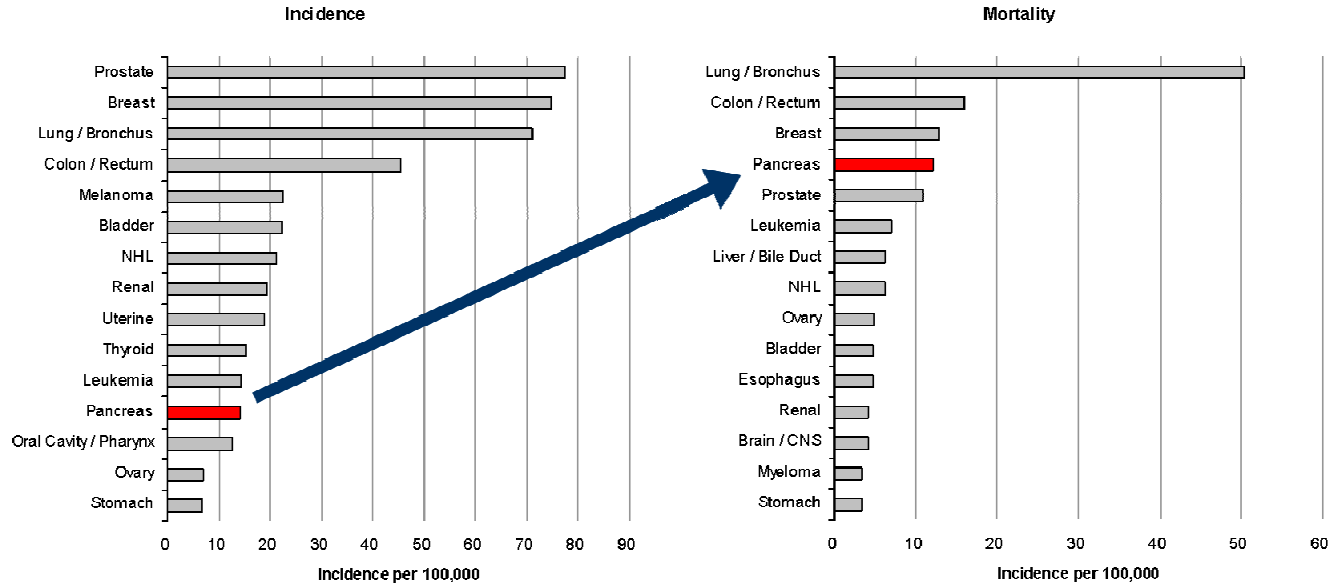
*ca*100K case of pancreatic cancer are diagnosed each year in the U.S. and EU and is the 4th leading case of cancer-related deaths

Pancreatic cancer is a deadly disease with annual incidences of *ca*37,000 in the U.S. (American Cancer Society) and *ca*40,000 in the EU (European Cancer Observatory). Of all cancers in the U.S., pancreatic cancer has the 12th highest incidence, but is the 4th leading cause of death. Exhibit 5 shows the incidence and mortality for pancreatic cancer relative to other cancers in the U.S.

Pancreatic cancer can be classified into two categories, exocrine or endocrine, based on the origin of abnormal cell growth.

- Exocrine tumors begin in cells that produce digestion enzymes, and account for ~95% of cases. The major type of exocrine pancreatic cancer is adenocarcinoma (a collection of cells surrounding an empty space) of ductal epithelium (cells lining the pancreatic duct), which accounts for ~75% of all pancreatic cancers. This type of pancreatic cancer is also generally regarded as one of the most aggressive cancers.
- Endocrine tumors start in cells that produce hormones, and make up the remaining ~5% of all cases. Endocrine tumors are generally slower growing than endocrine tumors. Endocrine tumors can be further categorized as functional or non-functional, which describe the ability of the cells to produce hormones. Most functional tumors are benign whereas the majority of non-functional tumors are malignant.

**Exhibit 5: Estimated Incidence and Mortality Rates of Major Cancers in the U.S. (2011)**




*Sources: American Cancer Society, Credit Suisse Research*

Most patients are typically diagnosed when the pancreatic cancer has progressed to the late stages due to the asymptomatic nature of early stage pancreatic cancer. Symptoms that lead to diagnosis of late-stage pancreatic cancer include jaundice, abdominal / back pain, weight loss, and loss of appetite. At the time of diagnosis, ~50% are metastatic, ~35% are locally advanced, and ~15% have resectable disease. In general, survival for patients with pancreatic cancer is very low. The median survival is ~6 months for metastatic disease and increases to ~15 months for resectable disease. Exhibit 6 shows the percentage of and survival for the three stages of pancreatic cancer.

Pancreatic cancer is typically diagnosed late and median survival for most patients is 6-9 months

**Exhibit 6: Disease Stage Distribution and Survival at Time of Diagnosis in the U.S.**

| Disease Stage | Patients at Diagnosis | Median Survival |
|---|---|---|
| Metastatic | 50% | 6 months |
| Locally Advanced | 35% | 9 months |
| Resectable | 15% | 15 months |

*Sources: Clovis, Credit Suisse estimates*

Significant unmet medical needs remain in pancreatic cancer, especially in patients with locally advanced and metastatic pancreatic cancer. There has been no improvement in survival for patients with locally advanced and metastatic pancreatic cancer for the last 15 years. The 1-year and 5-year survival rates are 26% and 6% respectively across patients with pancreatic cancer at all stages. Survival decreases significantly as the pancreatic cancer advances to later stages. For locally advanced disease, the five-year survival rate is 23% whereas, for metastatic disease, the five-year survival rate is 2%.

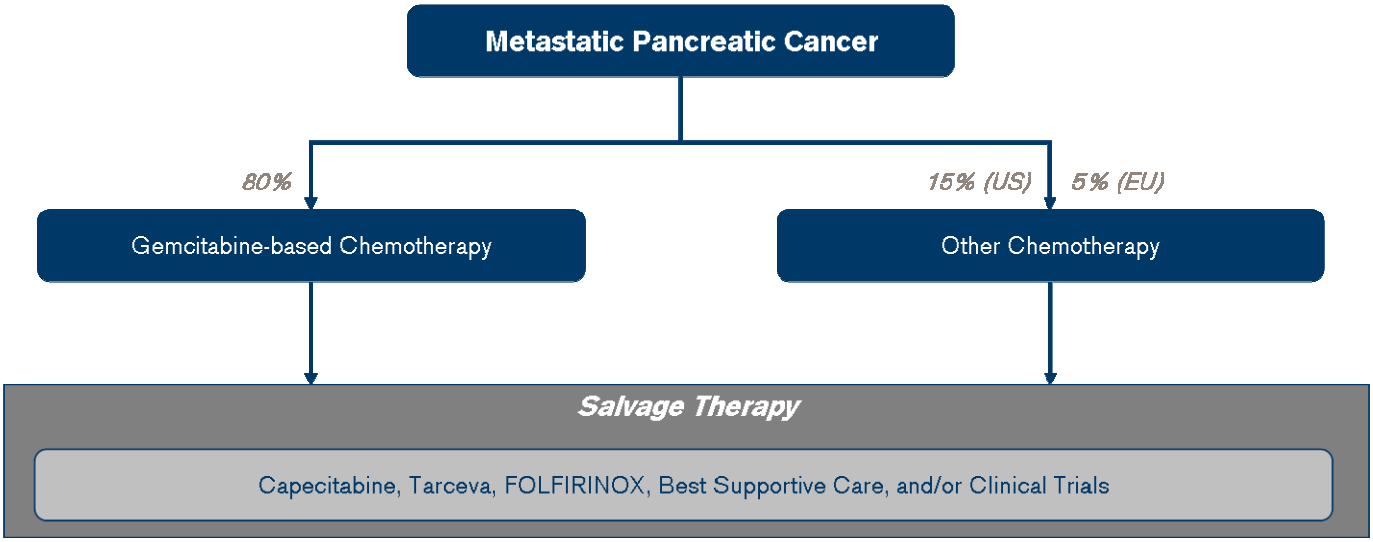
## Gemcitabine (Gemzar) is the standard-of-care in metastatic pancreatic cancer

The current standard-of-care treatment for pancreatic cancer depends on the stage of the disease. For resectable disease, oncologists surgically resect the tumor, and follow with adjuvant chemotherapy and/or radiation therapy. For locally advanced disease, oncologists typically start with chemotherapy and radiation therapy. In a small percentage of patients, the tumors shrink sufficiently, enabling physicians to surgically resect the remaining tumor. For metastatic disease, most oncologists use gemacitabine (i.e. Gemzar) as first-line therapy. It is estimated that *ca*80% of patients with metastatic pancreatic

Gemcitabine monotherapy is cornerstone first line treatment for metastatic pancreatic cancer, despite poor response rate

cancer in the U.S. and EU are treated with gemcitabine as first-line treatment. Some physicians may use the FOLFIRINOX regime, a combination treatment consisting of irinotecan, oxaliplatin, and either 5-fluorouracil or leucovorin. The second-line therapy options for patients with metastatic pancreatic cancer include capecitabine, capecitabine + Tarceva, and 5-fluorouracil + leucovorin + oxaliplatin. The current treatment paradigm for metastatic pancreatic cancer is presented in Exhibit 7.

**Exhibit 7: Current Treatment Paradigm for Metastatic Pancreatic Cancer**




*Sources: Clovis, Credit Suisse Research*

Gemzar (gemcitabine) was launched in the U.S. and EU in 1995 as a treatment for locally advanced or metastatic adenocarcinoma of the pancreas. In the U.S., gemcitabine was originally launched as a treatment investigational new drug before receiving formal approval from the FDA in May 1996. In the EU, gemcitabine was launched immediately following approval. Over the years, there have been new indications – metastatic breast cancer, non-small cell lung cancer, and advanced ovarian cancer – that have been added to the label. The indications for Gemzar in the U.S. and EU are provided in Exhibit 8.

Gemcitabine is also approved for metastatic breast cancer, non-small cell lung cancer, and advanced ovarian cancer

**Exhibit 8: Gemzar Indications in U.S. and EU**

| U.S. Label | EU Label |
|---|---|
| **Ovarian Cancer**<br>Used in combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy. | **Ovarian Cancer**<br>Indicated for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy. |
| **Breast Cancer**<br>Used in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated. | **Breast Cancer**<br>Used in combination with paclitaxel, is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated. |
| **Non-Small Cell Lung Cancer**<br>Used in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer. | **Non-Small Cell Lung Cancer**<br>Used in combination with cisplatin, is indicated as first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Gemcitabine monotherapy can be considered in elderly patients or those with performance status 2. |
| **Pancreatic Cancer**<br>Used as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemzar is indicated for patients previously treated with 5-FU. | **Pancreatic Cancer**<br>Used for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas. |
| **Bladder Cancer**<br>N/A | **Bladder Cancer**<br>Indicated for the treatment of locally advanced or metastatic bladder cancer in combination with cisplatin. |

*Source: Gemzar Package Inserts*

The separation in Kaplan-Meier curves between treatment (i.e., investigative drug) and comparator (i.e., standard-of-care drug) can be driven a subpopulation that respond more favorably to treatment with either the investigative or standard-of-care drug. For example, the efficacy seen the registrational clinical trials for Tarceva was driven primarily by a subpopulation of patients with L858R mutations in EGFR that responded very well to Tarceva and as a result, had better outcomes. Other examples of drugs in which certain patient populations experience more favorable responses include Herceptin (HER2neu), Zelboraf (BRAF V600E), and Xalkori (ALK). It is believed that response to gemcitabine in patients with pancreatic cancer could also be driven biomarkers. Studies have suggested that the levels of human nucleoside equilibrative transporter 1 (hENT1) could correlate with survival outcomes in patients with pancreatic cancer treated with gemcitabine.

## The hENT1 hypothesis – a predictor of clinical outcome

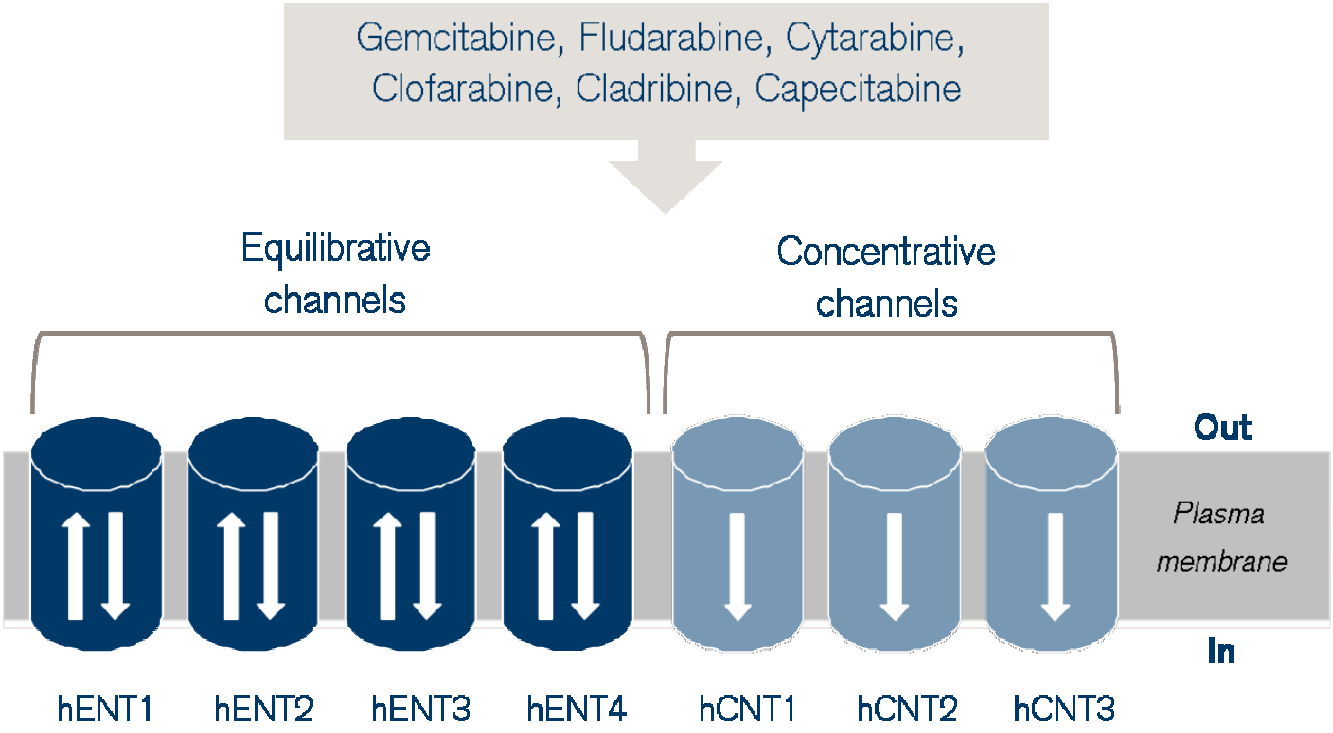
It is hypothesized that the clinical outcomes of gemcitabine is due to levels of a cell surface transported called hENT1

### What is hENT1?

hENT1 is a cell surface transporter required for the uptake of gemcitabine by tumor cells

Gemcitabine primarily enters tumor cells via human nucleoside equilibrative transporter 1 (hENT1), a member of a family of nuceloside transporters (NTs) as shown in Exhibit 9. Other NTs are believed to play a much smaller role in the uptake of gemcitabine by tumor cells. In general, hENT1 and other NTs are involved in the transport of nucleoside-based compounds (e.g. gemcitabine) into tumor cells. Studies have shown that other nucleoside-based drugs such as capecitabine, cladribine, clofarabine, cytarabine, and fludarabine generally require NTs to enter tumor cells.

**Exhibit 9: Role of hENT1 and Other Nucleoside Transporters in Delivering Drugs into Cancer Cells**




*Source: Clovis*

**How does hENT1 expression correlate to clinical outcome?**

Several independent studies have repeatedly supported the hENT1 hypothesis and the role of hENT1 in survival outcomes for pancreatic cancer:

- **Patients with low hENT1 have worse survival outcomes than patients with high hENT1 when treated with gemcitabine.** Studies have consistently shown that median overall survival in patients treated with gemcitabine is significantly shorter in the hENT1-low population than in the hENT1-high population. In addition, these studies have demonstrated that this correlation between hENT1 levels and survival breaks down in patients treated with non-gemcitabine therapies such as 5-FU.
- **The prevalence of low hENT1 in patients with pancreatic cancer is ~50%.** This estimate is supported by these studies, which have found that ~40-60% of patients with pancreatic cancer are hENT1-low.

In this section, we briefly describe the designs of and conclusions drawn from 5 studies examining correlations between hENT1 and survival outcomes in patients with pancreatic cancer treated with gemcitabine (summarized in Exhibit 10).

The hENT-1hypothesis is supported by 5 retrospective clinical studies that have correlated clinical outcomes with hENT-1 expression levels.....

**Exhibit 10: Summary of Results from hENT1 Studies**

| | Spratlin | Giovanetti | Farrell | Morinaga | Marechal |
|---|---|---|---|---|---|
| **Source** | Clinical Cancer Research 2004; 10: 6956-6961 | Cancer Research 2006; 66: 3928-3935 | Gastroenterology 2009; 136: 187-195 | ASCO 2011 | ASCO 2011 |
| **Year** | 2004 | 2006 | 2009 | 2011 | 2011 |
| **Patients Treated with Gemcitabine Evaluated for hENT1 Status** | 21 | 81 | 91 | 27 | 209 |
| **Disease Characteristics** | Stage I-II: N/A<br>Stage III-IV: 100% | Stage I-II: 44%<br>Stage III-IV: 56% | 100% Resectable | 100% Resectable | 100% Resectable |
| **hENT1 Status** | | | | | |
| hENT1-High | 43% | 46% | 37% | 59% | 38% |
| hENT1-Low | 57% | 54% | 43% | 41% | 62% |
| No hENT1 | N/A | N/A | 20% | N/A | N/A |
| **hENT1 Detection Technique** | IHC (Dako) | qPCR | IHC (Dako) | IHC | IHC |
| **hENT1 Scoring System** | - Scored based on uniformity of hENT1 staining relative to a reference<br>- High was given for uniformly stained tissue<br>- Low was given for tissue that had some regions with no staining | - Scored based on levels of hENT1 gene expression<br>- High was given for hENT1 expression levels above the median<br>- Low was given for hENT1 expression levels below the median | - Scored based on percentage of cells that were stained relative to a reference<br>- High was given for "strong" staining in >50% of cells<br>- None was given for no staining in >50% of cells<br>- Low was given for cases between High and None | - Scored based on evaluation of intensity of sample staining and percentage of positive tumor cells<br>- High was given for scores greater than or equal to median<br>- Low was given for scores less than median | - Scored based on evaluation of intensity of sample staining<br>- High was given for scores greater than median<br>- Low was given for scores less than median |
| **Overall Survival** | | | | | |
| Overall | 5 mo | N/A | N/A | N/A | N/A |
| hENT1-High | 13 mo | 22 mo | 21 mo | 22 mo | 51 mo |
| hENT1-Low | 4 mo | 12 mo | 16 mo | 12 mo | 24 mo |
| No hENT | N/A | N/A | 12 mo | N/A | N/A |
| **hENT1 High vs. Low p-Value** | 0.01 | <0.001 | 0.002 | 0.02 | <0.001 |

*Sources: Clovis, Credit Suisse analysis*

### Spratlin Study (2004)

The Spratlin study (2004) retrospectively examined 21 patients with metastatic pancreatic cancer treated with gemcitabine. The levels of hENT1 in tumor tissue samples were measured via IHC. The samples were scored based on the uniformity of staining relative to a reference of Langerhan cells and lymphocytes. "High" hENT1 was assigned to uniformly stained tissues with no heterogenous regions lacking any staining. "Low" hENT1 was given to tissues that had regions without any staining. This study showed that high-hENT1 patients lived longer than low-hENT1 patients. The median overall survival was 13 months for high-hENT1 patients and 4 months for hENT1-low patients (p=0.01).

### Giovanetti Study (2006)

The Giovanetti study (2006) retrospectively examined 81 patients with locally advanced and metastatic pancreatic cancer treated with gemcitabine. The hENT1 expression levels in tumor tissue samples were measured via quantitative polymerase chain reaction (qPCR). "High" hENT1 was assigned to samples with hENT1 expression levels above the median. "Low" hENT1 was given to samples with hENT1 expression levels below the median. This study demonstrated that hENT1-high patients had better survival outcomes than hENT1-low patients. The median overall survival was 22 months for high-hENT1 patients and 12 months for hENT1-low patients (p<0.001).

**Farrell Study (2009)**

The Farrell study (2009) was a prospective, randomized trial that enrolled 538 patients who had surgical resections of the pancreatic tumor. These patients were randomly assigned to receive either gemcitabine or 5-FU. The levels of hENT1 were only examined in 198 of the 538 patients treated with either gemcitabine or 5-FU. The levels of hENT1 were assessed via IHC. The tumor tissue samples were scored based on the percentage of cells stained relative to a reference of lymphocytes. “High” hENT1 was given if >50% of cells were strongly stained. “None” hENT1 was assigned if >50% of cells were not stained. “Low” hENT1 was used for cases between “None” and “High”. The major conclusions for this study are:

- This study showed that patients with high hENT1 had better survival outcomes than patients with low or no hENT1. The median overall survivals of patients with no, low, and high hENT1 are 12, 16, and 22 months respectively.
- This study also showed that there is no correlation between hENT1 levels and survival outcomes in patients treated with non-gemcitabine therapies. In patients treated with 5-FU, there was no difference in survival between hENT1-high and hENT1-low patients.

**Morinaga Study (2011)**

Morinaga’s study (2011) involved 27 patients with resected pancreatic adenocarcinoma treated with gemcitabine and 8 gemcitabine-naïve patients with pancreatic cancer. All patients were treated with curative resection followed by adjuvant gemcitabine. The levels of hENT1 were examined via IHC. The tumor tissue samples were scored based on the staining intensity and percentage of positive tumor cells. “High” hENT1 was given for scores above or equal to the median. “Low” hENT1 was assigned for scores below the median. The conclusions from this study include:

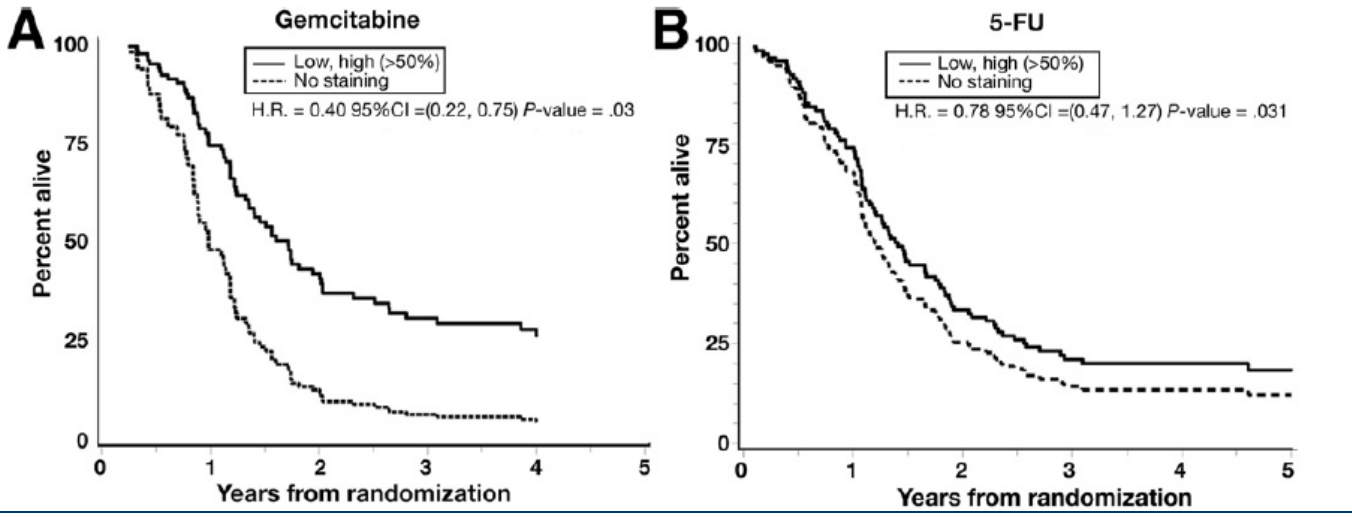
- The level of hENT1 expression does appear to correlate with overall survival and disease free survival in patients who were treated with gemcitabine.
- The median overall survival was 11.8 months in patients with low hENT1 as compared to 22.2 months in patients with high hENT1 (p=0.02).
- The median disease-free survival was 7.3 months in patients with low hENT1 as compared to 9.3 months in patients with high hENT1 (p=0.04).

**Maréchal Study (2011)**

Maréchal’s study (2011) recruited 434 patients with resected pancreatic adenocarcinoma and no prior neoadjuvant therapy. The hENT1 levels of each sample was examined via IHC. Each sample was characterized as either “high” or “low” based on the intensity of the staining. Of the 434 patients, 243 were given gemcitabine-based treatments, 49 were treated with non gemcitabine-based therapy and 142 did not receive any therapy. The conclusions from this study include:

- The level of hENT1 expression strongly correlates with overall survival in patients who were treated with gemcitabine. Patients with high levels of hENT1 expression had a median overall survival of 51 months as compared to 24 months for patients with low levels of hENT1 expression (p<0.001).
- Gemcitabine does not provide a survival benefit for patients with low levels of hENT1 expression. In the population with low levels of hENT1 expression, the difference in survival between patients who were treated with gemcitabine and patients who did not receive any therapy was not statistically significant (p=0.66)

**Exhibit 11 Kaplan-Meier Curves from Maréchal Study**




*Source: Clovis*

The guiding principal of the CO-101 hENT-1 LEAP study is to prospectively test the above described hENT1-hypothesis and attain accurate information on hENT-1 level expression and clinical outcome is a prospective study.

## CO 101 – What is it and how does it work?

**Background**

CO-101 is a lipid conjugated form of gemcitabine. CO-101 has the same mechanism of action as gemcitabine. However, unlike gemcitabine, CO-101 can bypass hENT1 to enter tumor cells. Clovis licensed global development and commercial rights of CO-101 from Clavis Pharma ASA (CLAVIS). Clavis develops compounds that are synthesized using its Lipid Vector Technology, which chemically links specific lipid chains to parent drugs.

CO-101 uses proprietary technology to make a lipid conjugated gemcitabine

The lead indication for CO-101 is first-line treatment of metastatic pancreatic cancer with low hENT1 levels. A follow-on indication for CO-101 could be second-line treatment of metastatic pancreatic cancer. CO-101 also could potentially be used for treating other solid tumors (See Appendix).

## Clinical and pre-clinical studies

**LEAP Study: PII/III Potential Pivotal Study**

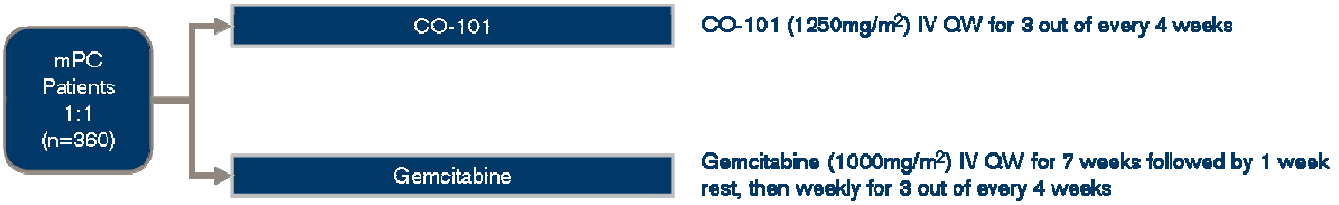
The **L**ow h**E**NT1 and **A**denocarcinoma of the **P**ancreas (LEAP) trial is a pivotal Phase II/III trial designed to evaluate the efficacy and safety of CO-101 relative to gemcitabine as a first-line treatment for patients with metastatic pancreatic adenocarcinoma. The trial plans to enroll 360 patients across 96 centers in 13 countries. Specifically, this study enrolled chemo-naïve patients with metastatic pancreatic ductal adenocarcinoma (i.e. stage IV) who provide sufficient pancreatic tumor tissue samples. Patients are randomized in a 1:1 fashion to receive either CO-101 or gemcitabine. In the CO-101 arm, patients are given 1250 mg/m$^2$ of CO-101 given intravenously once per week for 3 weeks in a 4-week cycle. In the gemcitabine arm, patients are treated with 1000 mg/m$^2$ intravenously on a weekly basis for 7 weeks followed by 1 week of rest, then weekly for 3 weeks in a 4-week cycle. The primary endpoint is overall survival in the hENT1-low population. The secondary endpoints include overall survival in the high hENT1-high population, objective response

LEAP prospectively tests:
(1) Response of both hENT1 low and high patients to CO101

(2) Extent in which response to gemcitabine is dependent on level of hENT1 expression

rate, duration of response, and progression free survival as defined by RECIST 1.1. Other secondary endpoints include CA 19-9 response rate, pain severity, health status, and pharmacokinetic profile. The design of the trial is presented in Exhibit 12.

**Exhibit 12: CO-101 LEAP Phase II/III Trial Design**




| | |
|---|---|
| **Purpose** | - Compare efficacy and safety of CO-101 to Gemcitabine as first-line therapy in mPC patients |
| **Patient Population** | - Chemo-naïve, metastatic pancreatic ductal adenocarcinoma (i.e. Stage 4) patients<br>- Must have sufficient amount of obtainable, metastatic tissue for later hENT1 analysis |
| **Primary Endpoint(s)** | - Overall survival with low hENT1 expression |
| **Secondary Endpoint(s)** | - Overall survival with high hENT1 expression<br>- Objective response rate<br>- Duration of response<br>- Progression-free survival<br>- Others include CA19-9 response rates, pain severity, health status, and pharmacokinetic profile |
| **Trial Powering** | - Powered to detect near doubling (~3.7 mo) in overall survival between arms in low hENT1 patients |
| **Data Readout** | - Potential data read-out 4Q 2012 |

*Sources: www.clinicaltrials.gov, Clovis, Credit Suisse analysis*

This trial is ~95% powered to detect a near doubling in overall survival for CO-101 over gemcitabine in hENT1-low patients with metastatic pancreatic cancer. This study assumes that median overall survivals are 7.7 months for hENT1-low patients treated with CO-101 and 4.0 months for hENT1-low patients treated with gemcitabine. The rationale behind the assumptions used in this trial are discussed below.

- Gemcitabine is ineffective in hENT1-low patients with metastatic pancreatic cancer. This hypothesis is supported by conclusions from 5 independent studies examining hENT1 status and survival outcomes in patients with pancreatic cancer. These studies have consistently shown that hENT1-low patients have worse survival outcomes than hENT1-high patients when treated with gemcitabine.
- CO-101 is more effective than gemcitabine in treating hENT1-low patients with metastatic pancreatic cancer. The preliminary results from Clavis's abbreviated Phase II trial provides some support to this assumption. In hENT1-low patients with metastatic pancreatic cancer, the median overall survival for the CO-101 arm was 9.1 months as compared to 3.3 months for the gemcitabine arm. This view is also supported by preclinical studies that have showed CO-101 can enter tumor cells without hENT1. In contrast, gemcitabine primarily enters tumor cells through hENT1.
- The estimate of 4.0 months is based on the historically observed median overall survival in patients with metastatic pancreatic cancer treated with best supportive care. This value is further supported by the median overall survival of 4.4 months in patients with metastatic pancreatic cancer treated with 5-FU from the pivotal study for gemcitabine.
- The estimate of 7.7 months in hENT1-high patients is inferred from the estimate of 4.0 months in hENT1-low patients. This survival difference represents a hazard ratio of 0.53. This hazard ratio is supported by conclusions from 5 independent studies (discussed above), preliminary results from Clavis's abbreviated Phase II trial, and reproduction of Farrell's results in Clovis's Study 002 (discussed below).

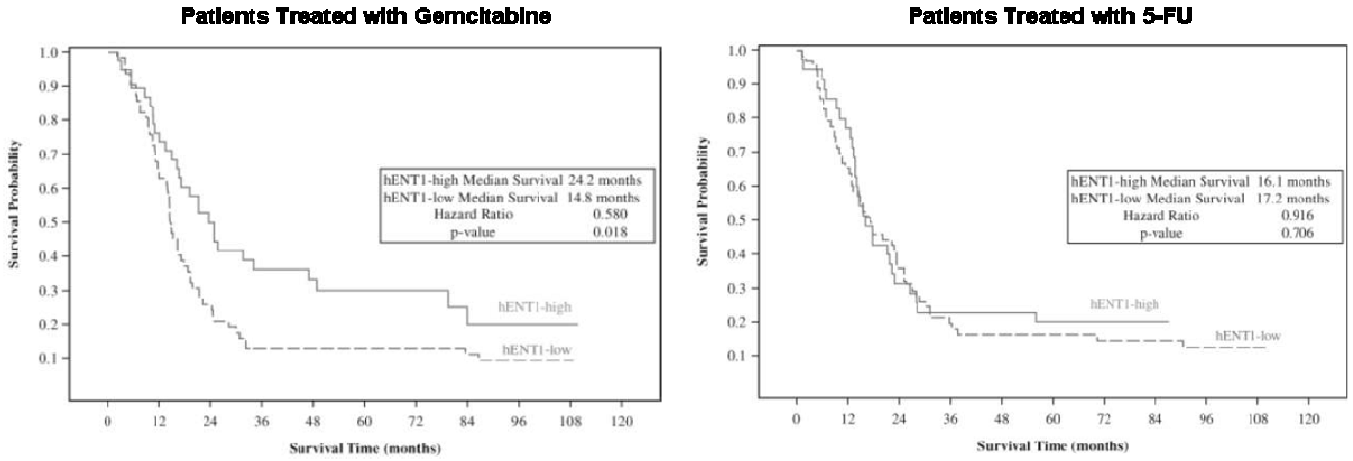
# Study 002: Observational Tissue Study

Study 002 established the hENT1 cut off to be used prospectively in the LEAP study

Study 002 is a retrospective study to define robust cut-offs for hENT1-high and hENT1-low using Ventana's IHC diagnostic test. The cut-off determined from this study was used to prospectively identifying hENT1-low patients in the LEAP study. In this study, Clovis examined pancreatic tissue samples from the Farrell et al. study, which compared the efficacies of gemcitabine and 5-FU in patients with pancreatic cancer. Ultimately, Clovis devised a hENT1 scoring system based on intensity of staining and amount of area stained.

This study demonstrated that hENT1 levels only correlate with efficacy in patients treated with gemcitabine. In patients treated with gemcitabine, the median overall survival for hENT1-high was 24.2 months, which was nearly twice the median overall survival of 14.8 months for hENT1-low (HR: 0.58, p=0.018). In contrast, this difference in survival by hENT1 levels was not observed in patients treated with 5-FU. In patients treated with 5-FU, the median overall survival was 16.1 months for hENT1-high as compared to 17.2 months for hENT1-low (HR: 0.916, p=0.706). The Kaplan-Meier plots for patients treated with gemcitabine and 5-FU segmented by hENT1 levels are presented in Exhibit 13.

**Exhibit 13: Kaplan-Meier Plots for Patients Treated with Gemcitabine and 5-FU Segmented by hENT1 Status**



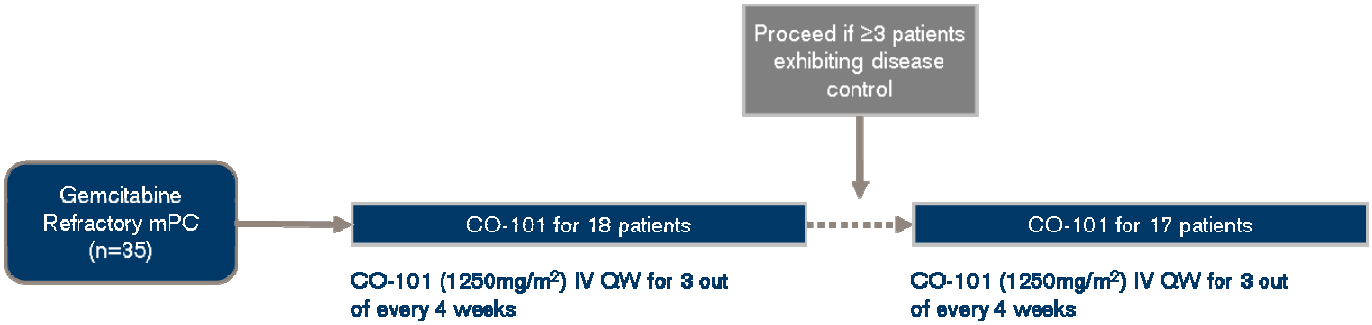

*Source: Clovis*

# Study 003: 2nd Line Pancreatic Cancer

This is a single arm study in hENT-1 absent patients that have failed standard 1st line therapy – read out due late 2013

Study 003 is an open-label, single-arm, two-stage Phase II trial for evaluating CO-101 as a second-line treatment in patients with metastatic pancreatic cancer who progressed following treatment with gemcitabine and had no presence of hENT1 as measured via Ventana's IHC diagnostic test. Patients are to be treated with 1250 mg/m$^2$ of CO-101 administered intravenously once per week for 3 weeks in a 4-week cycle. This trial consists of two stages. The first stage involves 18 patients. If ≥3 of the 18 patients treated with CO-101 exhibit disease control, then the second stage begins. In the second stage, the remaining 17 patients are treated with CO-101. The primary endpoint of this study is disease control rate (complete response, partial response, or stable disease) as defined by RECIST 1.1. The secondary endpoints include overall response rate, CA 19-9 response rate, progression-free survival, safety and tolerability, overall survival, and duration of response. The design of the trial is presented in Exhibit 14.

**Exhibit 14: CO-101 Study 003 Trial Design**




| | |
|---|---|
| **Purpose** | - Evaluate safety and efficacy of CO-101 as treatment for gemcitabine-refractory metastatic pancreatic cancer |
| **Patient Population** | - Gemcitabine-refractory, metastatic pancreatic ductal adenocarcinoma (i.e. Stage 4) patients<br>- Treated with >3 doses of gemcitabine (as monotherapy or combination therapy)<br>- Must have sufficient amount of obtainable, metastatic tissue for later hENT1 analysis |
| **Primary Endpoint(s)** | - Disease control rate using RECIST 1.1 |
| **Secondary Endpoint(s)** | - Overall survival<br>- Progression free survival<br>- Duration of response<br>- Overall response rate,<br>- Safety and tolerability<br>- Others include CA 19-9 response rate |
| **Data Readout** | - Potential data read-out in 2013 |

*Sources: www.clinicaltrials.gov, Clovis, Credit Suisse analysis*

## Other Potential Future Studies with CO-101

CO-101 could potentially be evaluated in other solid tumors in conjuction with hENT1 expression. CO-101 could be examined in cancers indicated in the label for gemcitabine in the U.S. and EU including bladder cancer, metastatic breast cancer, ovarian cancer, and non-small cell lung cancer (NSCLC). Studies have suggested that levels of hENT1 expression could be used to assess efficacy of gemcitabine in combination with cisplatin for treatment of NSCLC.

The hENT-1 hypothesis should also be applicable to NSCLC, ovarian and breast cancer

## Phase I Trial: First-In-Man Study

Clavis conducted a dose-escalation Phase I trial for CO-101 in 43 patients with colorectal cancer, pancreatic cancer, ovarian cancer, and/or other advanced solid tumors. The purpose of this trial was to determine the recommended and maximum tolerated doses of CO-101 and evaluate the safety profile of CO-101. This ascending dose study involved 10 cohorts that examined the following doses of CO-101: 30, 60, 120, 240, 480, 800, 1000, 1250, 1400, and 1600 mg/m$^2$ given weekly for 3 weeks in a 4-week cycle. The level of hENT1 expression in patients was not examined. The trial was performed in sites located in Oslo, Brussels, and Glasgow. All patients completed treatment with CO-101 by December 2009.

A 43 patient PI study conducted in 2009 safety and a standard 1250 mg/m$^2$ dose

This trial enabled Clavis to find the right dose of CO-101 for future trials. In addition, this study demonstrate that CO-101 was generally well-tolerated and potentially effective in treating advanced solid tumors. The major conclusions from this trial are presented below.

- The recommended dose for all future studies was determined to be 1250 mg/m$^2$. The concentration of gemcitabine in plasma at 1250 mg/m$^2$ of CO-101 (AUC: 26.6 μM·h) was higher than that for the standard dose of 1000 mg/m$^2$ of gemcitabine (AUC: 14.3 μM·h). In addition, CO-101 was dose-proportional with Cmax and AUC at doses of 400-1600 mg/m$^2$. Exhibit 15 lists the Cmax, AUC, and half-life for CO-101 and gemcitabine.

- CO-101 was generally safe and well-tolerated, demonstrating a similar side effect profile to gemcitabine. The most common grade 3/4 adverse events caused by CO-101 were neutropenia (16% of patients at 1250 mg/m$^2$ CO-101) and fatigue (which was the DLT). The following dose-limiting toxicities were observed: grade 3 fatigue (2 events; 1,400 mg/m$^2$), thrombocytopenia (1 event; 800 mg/m$^2$), death due to acute lung damage (1 event; 1,000 mg/m$^2$), grade 3 elevated AST/ALT levels (1 event; 1,600 mg/m$^2$), and grade 4 neutropenia (1 event; 1,600 mg/m$^2$). The top-5 most frequent common grade 1/2 adverse events were nausea, fatigue, vomiting, anorexia, and lethargy. Myelosuppression was also observed in this trial. These toxicities are generally similar to that observed with gemcitabine.
- Treatment with CO-101 led stabilization of disease in 7 patients with colorectal, ovarian, and pancreatic cancer for >3 months. Of these 7 patients, 2 patients with pancreatic cancer previously treated with gemcitabine were given ≥5 cycles of CO-101 and had stable disease for ≥5 months.

**Exhibit 15: Plasma Levels after IV Administration of CO-101 and Gemcitabine**

***Plasma dFdC after iv administration of CO-101 or gemcitabine (dFdC)***

| | Cmax (µM) | AUC $_{0\text{-}\infty}$ (µM.h) | Half-life (hrs) |
|---|---|---|---|
| CO-101 | | | |
| 1250mg/m$^2$ | 37.8 | 26.6 | 0.25 |
| Gemcitabine* | | | |
| 960mg/m$^2$ | 38.9 | 14.3 | 0.11 |
| 640mg/m$^2$ | 23.4 | 9.8 | 0.12 |

Administered dose includes 625 mg/m$^2$ gemcitabine + 625 mg/m$^2$ lipid

*Source: Clovis*

## Abbreviated Phase II Study

A small 21 patient PII study showed results consistent with the hENT1 hypothesis

Clavis initiated an open-label Phase II study to evaluate CO-101 as a potential treatment for pancreatic cancer in June 2009. This trial only involved centers based in Europe. After Clovis obtained rights to CO-101 from Clavis, both companies decided to stop this trial early (at this point, 21 patients had been treated with either CO-101 or gemcitabine, 10 under the pilot phase with CO-101 only, 11 under randomized part CO-101 vs. gemcitabine). Clovis and Clavis planned to start the LEAP study, which was designed to bring CO-101 to market faster – as previously discussed the overall survival endpoint (and testing of the hENT-1 hypothesis) allows LEAP to be used as a pivotal study.

The Phase II trial intended to evaluate CO-101 in 40 chemo-naïve patients with locally advanced and metastatic pancreatic adenocarcinoma. Patients were to be treated with 1250 mg/m$^2$ of CO-101 given intravenously once per week for 3 weeks in a 4-week cycle. The level of hENT1 expression was examined in this trial. In July 2009, this study was amended to allow for randomization of patients for treatment with either CO-101 or gemcitabine after enrollment of the first 10 patients. The primary endpoint was change in CA-19-9, a tumor marker. The secondary endpoints were overall survival and overall response rate as defined by standard RECIST criteria. Exhibit 16 summarizes the results from this study.

**Exhibit 16: Efficacy Data from Abbreviated Phase II Study (21 Patients)**

| | Patient Group | Number of Patients | Median Overall Survival | Hazard Ratio | Comments |
|---|---|---|---|---|---|
| CO-101 | All | 14 | 7.6 months | 0.44 | CO-101 had a modest survival advantage of 1.6 months in patients with metastatic pancreatic cancer. |
| Gemcitabine | All | 4 | 5.9 months | | |
| CO-101 | hENT1-Low | 3 | 9.1 months | N/A | CO-101 had a significant survival advantage of 5.8 months in the subset of hENT1-low patients |
| Gemcitabine | hENT1-Low | 1 | 3.3 months | | |

*Source: Clovis, Credit Suisse analysis*

Notwithstanding the small study size, the signal of CO-101 in hENT1 low patients (vs. gemcitabine) was notable

The data from the Phase II trial suggested that CO-101 could be more effective than gemcitabine in treating patients with hENT1-low metastatic pancreatic cancer. This patient subpopulation from the Phase II study is comparable to the patient population being examined in the LEAP study. In all patients, CO-101 provided a survival advantage of 1.7 months. The median overall survival was 7.6 months for patients treated with CO-101 as compared to 5.9 months for patients treated with gemcitabine (HR: 0.44). In hENT1-low patients, the median overall survival for patients treated with CO-101 was 9.1 months, which was longer than 3.3 months for patients given gemcitabine. In hENT1-high patients, CO-101 did not appear to offer a survival benefit over gemcitabine.

CO-101 appears to have a side effect profile that is consistent with gemcitabine. Overall, there were 33 grade 3/4 adverse events, with the most frequent one being neutropenia. The dosage of CO-101 was reduced in some patients due to neutropenia and thrombocytopenia. The most common treatment-emergent adverse event (TEAE) was nausea and/or vomiting, which occurred in >50% of patients treated with CO-101. The incidence of this TEAE was higher in the CO-101 arm as compared to gemcitabine arm.

## CO-101 – Intellectual Property

Our base case scenario is IP protection until at least 2020 and 2023 in US and EU respectively, however...

We expect CO-101 will likely be protected from generic competition until at least 2020 in the U.S. and 2023 in the EU. The primary mechanism of protection is extension of on the life of the composition of matter patents for CO-101. In the U.S., this patent will likely be extended from 2018 to 2020-2021 due to the Hatch-Waxman Act. In the EU, with the supplementary protection certificate, the patent could be extended from 2018 to 2023. Another mechanism for protecting CO-101 includes orphan drug designation in the U.S. and EU.

...formulation patents could extend protection until 2030

There is the potential for CO-101 to be protected until at least 2030 via the formulation patent on CO-101. The rationale behind this view is based on the expectation that generic companies will have a difficult time circumventing the complexity and narrowness of the claims in the formulation patent.

- The patent defines a very narrow range of drug-to-lipid ratio for making stable particles. In general, it is extremely difficult to get CO-101 into solution. The use of a drug-to-lipid ratio outside of the range defined in the patent leads to formation of unstable particles or precipitation.
- The patent covers use of all standard lipids for creating stable particles of CO-101. Generic companies will be reluctant to use new, novel lipids to solubilize CO-101, as this route will require additional clinical trials.

Exhibit 17 lists the primary patents associated with CO-101.

Exhibit 17: **Primary Patents for CO-101**

| U.S. | | | |
|---|---|---|---|
| **Patent Type** | **Original Expiration** | **Potential Expiration with Extensions** | **Status** |
| Composition # 6,384,019 | 2018 | 2020-2021 (Hatch-Waxman Act) | Issued |
| Formulation | 2030 | >2030 | Pending |
| **EU** | | | |
| **Patent Type** | **Original Expiration** | **Potential Expiration with Extensions** | **Status** |
| Composition # 6,384,019 | 2018 | 2023 | Issued |
| Formulation | 2030 | >2030 | Pending |

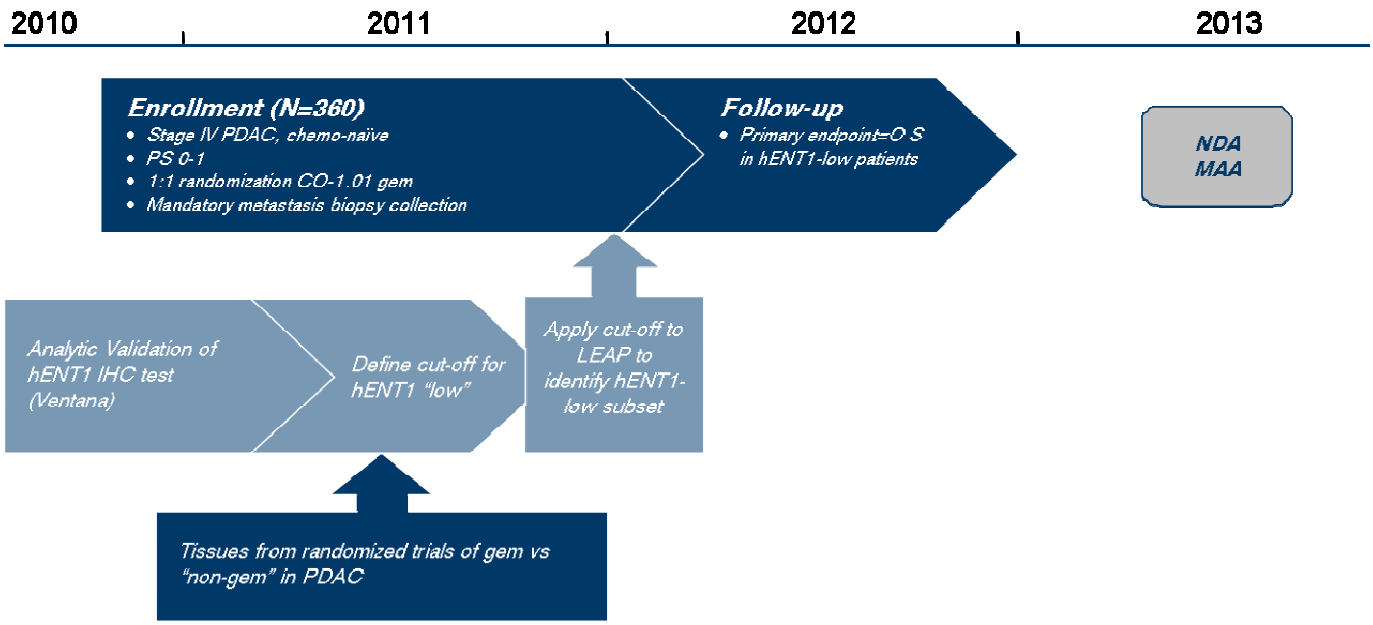
*Source: Clovis, Credit Suisse Research*

## Regulatory strategy and timeline summary for CO-101

The timeline for development of CO-101 is presented in Exhibit 18. The key milestones include: 1) Application of the cut-off for defining low and high hENT1 in patients from LEAP study by the end of 2011; 2) Potential data readout in the primary endpoint from the LEAP trial in Q4 2012; and 3) NDA / MAA filing for CO-101 in 2013.

LEAP is due to readout in Q4 2012 with a potential filing in 2013

Exhibit 18: **CO-101 LEAP Trial Timeline**




*Source: Clovis*

## Ventana hENT1 Assay

Ventana's hENT1 immunohistochemistry (IHC) kit is commercially available in the Europe as a class 1 *in vitro* diagnostic. It received a CE mark in December 2010. Ventana has an exclusive license to both the anti-hENT1 antibody and hybridoma cell line for producing the anti-hENT1 antibody from Clavis. This assay uses hENT1 for qualitative staining of formalin-fixed, paraffin-embedded tissue from the adrenal gland, kidney, pancreas, and lymph nodes. The test is used on Ventana's BenchMark Series automated slide stainer.

Ventana (part of Roche) has developed and will market the hENT1 kit

Ventana plans to commercialize a companion diagnostic to CO-101 based on the hENT1 IHC kit and the protocol developed by Clovis to identify patients as hENT1-high or hENT1-low. Ventana plans to obtain a PMA for this companion diagnostic simultaneously with the

NDA / MAA approval of CO-101. Ventana plans to commercialize the companion diagnostic worldwide.

## Competitive Landscape

Several compounds are being examined for pancreatic cancer in clinical trials. Exhibit 19 lists active compounds in the late-stage pipeline. Of the compounds being studied as a first-line treatment in patients with metastatic pancreatic cancer, nearly all are being evaluated in combination with gemcitabine in a general population with metastatic pancreatic cancer. None of these studies are explicitly examining how hENT1 status affects patients outcomes.

Almost all other drugs in development for PC are in combination with gemcitabine and do not test the hENT1 hypothesis

**Exhibit 19: Late-Stage Pipeline for Pancreatic Cancer**

| Compound | Company | Regimen | Phase | Indication(s) | Route of Administration | Mechanism of Action Comments |
|---|---|---|---|---|---|---|
| Abraxane | Celgene | + GEM | III | 1st-Line mPC | Intravenous | Nanoencapsulated Paclitaxel |
| Ganitumab | Amgen | + GEM | III | 1st-Line mPC (PIII)<br>1st-Line LAPC (PII) | Intravenous | Anti-IGF-1 mAb |
| GV1001 | KAEL | + GEM + CAP | III | mPC (PIII)<br>LAPC (PIII) | Intradermal | Telomerase Peptide Vaccine |
| HyperAcute | Newlink | + GEM +/- 5-FU | III | srPC | Intradermal | Immunotherapy |
| Masitinib | AB Science | + GEM | III | mPC | Oral | FGFR, KIT, PDGFR Inhibitor |
| PEP02 / MM-398 | Merrimack | None | III | 2nd-Line mPC | Intravenous | Nanoencapsulated Irinotecan |
| S-1 (Japan/Taiwan Only) | Otsuka | + GEM | III | 1st-Line | Oral | Prodrug of 5-FU |
| Estybon | Onconova | + GEM | II/III | 1st-Line mPC | Oral | Plk1 / PI3K / AKT Inhibitor |
| Nimotuzumab | YM Bio | None | II/III | 2nd-Line mPC | Intravenous | Anti-EGFR mAb |
| Clivatuzumab | Immunomedics | + GEM | I/II | 1st-Line mPC<br>1st-Line LAPC | Intravenous | MUC-1 |

CAP = Capecitabine; GEM = Gemcitabine; 5-FU = 5-Fluorouracil
LAPC = Locally Advanced Pancreatic Cancer, mPC = Metastatic Pancreatic Cancer, srPC = Surgically Resected Pancreatic Cancer
*Source: BioMedTracker, Credit Suisse analysis*

In general, the addition of each compound to gemcitabine increases survival in the general population of patients with metastatic pancreatic cancer based on Phase II trials. The combination regimen consisting of 125 mg/m$^2$ Abraxane and 1000 mg/m$^2$ gemcitabine had a median overall survival of 12.2 months, which is nearly two-times as long 6 months for the historical overall survival for gemcitabine. The addition of 12 mg/kg ganitumab increased median overall survival to 8.7 months, which is 1.8 month longer than 5.9 months for the control arm treated with 1000 mg/m$^2$ gemcitabine monotherapy. The use of 1200-1800 mg/m$^2$ Estybon with 1000 mg/m$^2$ gemcitabine had a median overall survival of 11.1 months (vs. 6 months for the historical overall survival for gemcitabine. The addition of clivatuzumab to 200 mg/m$^2$ gemcitabine had a median overall survival of 7.7 months (vs. 6 months for the historical overall survival for gemcitabine). In patients who received multiple treatments of clivastuzumab, the median overall survival in this subpopulation was 11.8 months. Exhibit 20 lists the more recent clinical data available for each compound.

PII results of several investigation drugs in PC have demonstrated survival extensions

From a safety perspective, the addition of each investigative compound to gemcitabine appears to increase incidence of adverse events and/or introduce new side effects. The use of Abraxane and gemcitabine increased the incidence of grade 3 neutropenia to 30% (vs. 17% from the Phase III trial for gemcitabine) and grade 4 neutropenia (vs. 7% from the Phase III trial for gemcitabine). Addition of ganitumab on top of gemcitabine appeared to increase the incidence of thrombocytopenia and fatigue to 15% (vs. 8% for the gemcitabine arm), 13% (vs. 5% for the gemcitabine arm). For Estybon, we do not know

how the incidence on side effects has been affected given the most recent data came from a small Phase I trial.

**Exhibit 20: Phase II Efficacy and Safety Data for Abraxane, Ganitumab, and Estybon**

| | Abraxane | Ganitumab | Estybon | Clivtuzumab |
|---|---|---|---|---|
| **General** | | | | |
| Phase of Trial | I/II | I/II | I | I/II |
| Number of Patients | 44 (Total: 67) | 40 (Total: 121) | 12 (Total: 36) | 38 (Total: 38) |
| Dosing | 125 mg/m$^2$ | 12 mg/kg | 1200 mg/m$^2$ | 6.5, 9.0, 12, or 15 mCi/m$^2$ |
| Regimen | + GEM | + GEM | + GEM | + GEM |
| Disease Type | mPC | mPC | mPC | mPC, LAPC |
| **Efficacy** | | | | |
| Median OS | 12.2 mo | 8.7 mo (vs. 5.9 mo pbo) | 11.1 mo | 7.7 mo |
| Median PFS | N/A | 5.1 mo (vs. 2.1 mo pbo) | 4.4 mo | |
| ORR | 50% | N/A | N/A | 16% |
| DCR | 68% | N/A | N/A | 58% |
| OS Rate at 6 mo | N/A | 57% (vs. 50%) | N/A | 58% |
| OS Rate at 12 mo | N/A | 39% (vs. 23%) | N/A | 26% |
| Other | 37% with >70% decrease in CA 19-9 levels | N/A | N/A | OS of 11.8 months in patients treated with more than once of clivatuzumab |
| **Safety** | | | | |
| Incidence | N/A | N/A | N/A | N/A |
| Common Adverse Events | 30% G3 Neutropenia<br>40% G4 Neutropenia<br>G3 Sensory Neuropathy<br>G3 Fatigue<br>G3/4 Thrombocytopenia | *Ganitumab*<br>18% Neutropenia<br>15% Thrombocytopenia<br>8% Abdominal Pain<br>13% Fatigue<br><br>*Placebo*<br>13% Neutropenia<br>8% Thrombocytopenia<br>13% Abdominal Pain<br>5% Fatigue | *All Patients with Different Types of Cancers*<br>Neutropenia<br>Thrombocytopenia<br>Elevated AST/ALT<br>Nausea<br>Vomiting<br>Fatigue | N/A |
| Other | 1 death | N/A | 1 death | N/A |

*Source: Amgen, Celgene, OncoNova, Credit Suisse estimates*

CO-101 will likely dominate investigational gemcitabine-based regimens as first-line treatment in patients with hENT1-low metastatic pancreatic cancer. It is important to note that we do expect physicians will likely use gemcitabine-based regimens (if approved) to some degree in their patients. The driver and limiters on the extent of use of CO-101 over these gemcitabine-based regimens is discussed below.

The usage of CO-101 over investigational gemcitabine-based regimens in patients with hENT1-low metastatic pancreatic cancer could be driven by the following factors.

- Physicians could be reluctant to use combination regimens involving gemcitabine due to a lack of demonstrated benefit. This hesitation stems from the fact that these combination regimens have not been evaluated in patients with hENT1-low metastatic pancreatic cancer, and that gemcitabine is not effective in treating patients with hENT1-low metastatic pancreatic cancer.
- The potential for increased side effects due to the addition of another compound on top of gemcitabine could encourage physicians to administer CO-101 over gemcitabine-based regimens. In general, drugs for treating cancer tend to be very toxic. Physicians will likely prefer to minimize side effects without sacrificing too much on efficacy.

However, if the investigational gemcitabine-based regimen is shown to be significantly efficacious, then usage of CO-101 in hENT1-low metastatic pancreatic cancer could be

limited. We expect this situation to hold true even if the gemcitabine-based regimen has not been explicitly examined in this patients population. With a high efficacy shown, physicians are likely to feel more comfortable using such gemcitabine-based regimens.

**Mid-Stage Pipeline**

Exhibit 21: **Mid-Stage Pipeline for Pancreatic Cancer**

| Compound | Company | Regimen | Phase | Indication(s) | Route of Administration | Mechanism of Action |
|---|---|---|---|---|---|---|
| AGS-1C4D4 | Astellas | + GEM | II | mPC (1st-Line) | Intravenous | PSCA mAb |
| Archexin | Rexahn | + GEM | II | mPC | Intravenous | PI3K/AKT Inhibitor |
| Bavituximab | Peregrine | + GEM | II | mPC (1st-Line) | Intravenous | Phosphatidylserine mAb |
| GVAX | Aduro | + CTX + CRS-207 + CTX | II | mPC, aPC | Intradermal | GM-CSF Expressing Immunotherapy |
| Capoxigem | Tragara | + GEM + ET | II | LAPC, mPC (1st-Line) | Oral | COX-2 Inhibitor |
| CRS-207 | Aduro | + GVAX + CTX | II | mPC | Intravenous | Mesothelin Expressing Immunotherapy |
| GI-4000 | GlobeImmune | + GEM | II | prNMPC | Subcutaneous | RAS Protein Expressing Immunotherapy |
| GSK1120212 | GSK | + GEM | II | 1st-Line mPC | Oral | MEK Inhibitor |
| INNO-206 | CytRx | Not Available | II | mPC (1st-Line) LAPC (1st-Line) | Intravenous | Doxorubicin with Acid Sensitive Linker |
| LE-DT | Insys | Monotherapy | II | mPC, LAPC | Intravenous | Liposomal-Encapsulated Paclitaxel |
| Nexavar | Bayer | + GEM + ET | II | mPC (1st-Line) | Oral | Kinase Inhibitor |
| PM01183 | PharmaMar | Monotherapy | II | mPC | Intravenous | DNA Minor Groove Binder |
| Reolysin | Oncolytics | + GEM + CDPP + PTX | II | aPC, mPC (1st-Line) rPC, mPC (1st-Line) | Intravenous | Respiratory Enteric Orphan Virus |
| Revlimid | Celgene | + GEM | II | mPC (1st-Line) | Oral | Antiangiogenic |
| Selumetinib | AstraZeneca | + ET | II | LAPC, mPC (1st-Line) | Oral | MEK Inhibitor |
| TH-302 | Threshold | + GEM | II | LAPC, mPC (1st-Line) | Intravenous | DNA Alkylator |

CAP = Capecitabine; CTX = Cyclophosphamide; ET = Erlotinib; GEM = Gemcitabine, PTX = Paclitaxel
LAPC = Locally Advanced Pancreatic Cancer, mPC = Metastatic Pancreatic Cancer
prNMPC = Previously Resected Non-Metastatic Pancreatic Cancers, srPC = Surgically Resected Pancreatic Cancer
mAb = Monoclonal Antibody, PSCA = Prostate Stem Cell Antigen

*Source: BioMedTracker, Credit Suisse analysis*

# Revenue model for CO-101

Our revenue model for CO-101 is shown in Exhibit 22. Our revenue estimates for CO-101 are driven by a patient model for locally advanced and metastatic pancreatic cancer in the U.S. and EU. Our key assumptions in the model include:

We model peak $345m peak sales for CO-101 – launch in 2014 and effective patent protection until 2021. We note numerous upside opportunities.

- 2011 incidence of pancreatic cancer in the U.S. and EU are 36,778 and 40,326 respectively and increases 2% annually.
- Percentage of patients with locally advanced and metastatic disease is 85%.
- Percentage of patients with hENT1-low status is 50%.
- Launch of CO-101 in the U.S. and EU in Q1 2014.
- Peak penetration is expected to occur in the U.S. in 2020. and in the EU in 2021.
- Worldwide peak sales of CO-101 are expected to be *ca*$645M in 2021.

- Price per month of CO-101 in the U.S. and EU is expected to be $4,481 and $3,361 in 2021. Patients would likely be treated with CO-101 for 7 months on average.
- Protection from generic competition in the U.S. is expected to last through 2021. The composition of matter patent expires in 2018, and is expected to be extended by 3 years via the Hatch-Waxman Act.
- Protection from generic competition in the EU is expected to last through 2023. The composition of matter patent expires in 2021, and is expected to be extended by 2 years via the supplementary protection certificate.
- As discussed latter in this note we see notable opportunity for effective patent term extension for CO-101, based on formation patents, but have not included them in our revenue assumption (or subsequent valuation)
- Rapid erosion of market share when patents expire due to expected generic competition.

**Exhibit 22: Clovis CO-101 Revenue Model**

| United States | 2011E | 2012E | 2013E | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E | 2020E | 2021E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pancreatic Cancer Prevalence | 36,778 | 37,514 | 38,264 | 39,029 | 39,810 | 40,606 | 41,418 | 42,247 | 43,092 | 43,953 | 44,833 |
| % Metastic / Advanced Local | *85%* | *85%* | *85%* | *85%* | *85%* | *85%* | *85%* | *85%* | *85%* | *85%* | *85%* |
| # Metastatic / Advanced Local | 31,262 | 31,887 | 32,525 | 33,175 | 33,838 | 34,515 | 35,206 | 35,910 | 36,628 | 37,360 | 38,108 |
| % hENT low | *50%* | *50%* | *50%* | *50%* | *50%* | *50%* | *50%* | *50%* | *50%* | *50%* | *50%* |
| # hENT low Patients | 15,631 | 15,943 | 16,262 | 16,587 | 16,919 | 17,258 | 17,603 | 17,955 | 18,314 | 18,680 | 19,054 |
| CO-101 Penetration | *0.0%* | *0.0%* | *0.0%* | *13.0%* | *23.0%* | *33.0%* | *43.0%* | *53.0%* | *63.0%* | *67.0%* | *67.0%* |
| Patients Treated with CO-101 | 0 | 0 | 0 | 2,156 | 3,891 | 5,695 | 7,569 | 9,516 | 11,538 | 12,516 | 12,766 |
| Price/Month | $4,057 | $4,097 | $4,138 | $4,180 | $4,222 | $4,264 | $4,306 | $4,349 | $4,393 | $4,437 | $4,481 |
| Average Number of Months on Therapy | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 |
| Price / Patient | $28,398 | $28,682 | $28,968 | $29,258 | $29,551 | $29,846 | $30,145 | $30,446 | $30,751 | $31,058 | $31,369 |
| **Total Revenue ($ '000)** | **$0** | **$0** | **$0** | **$63,092** | **$114,995** | **$169,975** | **$228,171** | **$289,728** | **$354,794** | **$388,715** | **$400,455** |

| EU | 2011E | 2012E | 2013E | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E | 2020E | 2021E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pancreatic Cancer Prevalence | 40,326 | 41,132 | 41,955 | 42,794 | 43,650 | 44,523 | 45,414 | 46,322 | 47,248 | 48,193 | 49,157 |
| % Metastic / Advanced Local | *85%* | *85%* | *85%* | *85%* | *85%* | *85%* | *85%* | *85%* | *85%* | *85%* | *85%* |
| # Metastatic / Advanced Local | 34,277 | 34,963 | 35,662 | 36,375 | 37,103 | 37,845 | 38,601 | 39,374 | 40,161 | 40,964 | 41,783 |
| % hENT low | *50%* | *50%* | *50%* | *50%* | *50%* | *50%* | *50%* | *50%* | *50%* | *50%* | *50%* |
| # hENT low Patients | 17,139 | 17,481 | 17,831 | 18,188 | 18,551 | 18,922 | 19,301 | 19,687 | 20,080 | 20,482 | 20,892 |
| CO-101 Penetration | *0.0%* | *0.0%* | *0.0%* | *8.5%* | *16.5%* | *24.5%* | *32.5%* | *40.5%* | *45.5%* | *47.5%* | *49.5%* |
| Patients Treated with CO-101 | 0 | 0 | 0 | 1,546 | 3,061 | 4,636 | 6,273 | 7,973 | 9,137 | 9,729 | 10,341 |
| Price/Month | $3,043 | $3,073 | $3,104 | $3,135 | $3,166 | $3,198 | $3,230 | $3,262 | $3,295 | $3,328 | $3,361 |
| Average Number of Months on Therapy | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 |
| Price / Patient | $21,298 | $21,511 | $21,726 | $21,944 | $22,163 | $22,385 | $22,609 | $22,835 | $23,063 | $23,294 | $23,527 |
| **Total Revenue ($ '000)** | **$0** | **$0** | **$0** | **$33,923** | **$67,840** | **$103,775** | **$141,817** | **$182,063** | **$210,718** | **$226,623** | **$243,298** |

*Source: Clovis, Credit Suisse estimates*

# CO-1686 (Oral EGFR Inhibitor)

Clovis is developing CO-1686, a oral small molecule inhibitor of mutant forms of EGFR, being developed for the treatment of NSCLC. The phase I study is due to initiate in H1 2012. Clovis has an accelerated development goal that could take CO-1686 from IND to NDA in around 4 years. In the appendix of this note we provide a backgrounder to lung cancer and current treatment paradigms.

Tarceva and Iressa are TKIs that are gold standard in the treatment of refractory NSCLC...

The tyrosine kinase inhibitors (TKIs), Tarceva and Iressa. were introduced in the early 2000s. TKIs were first launched in the U.S. and EU as a treatment for locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Iressa was brought to the U.S. and EU markets in 2003 and 2009 respectively. Tarceva was launched in the U.S. and EU in 2004 and 2005 respectively.

...and target initial activating EGFR mutations, notably L858R and exon 19 deletion mutations, however...

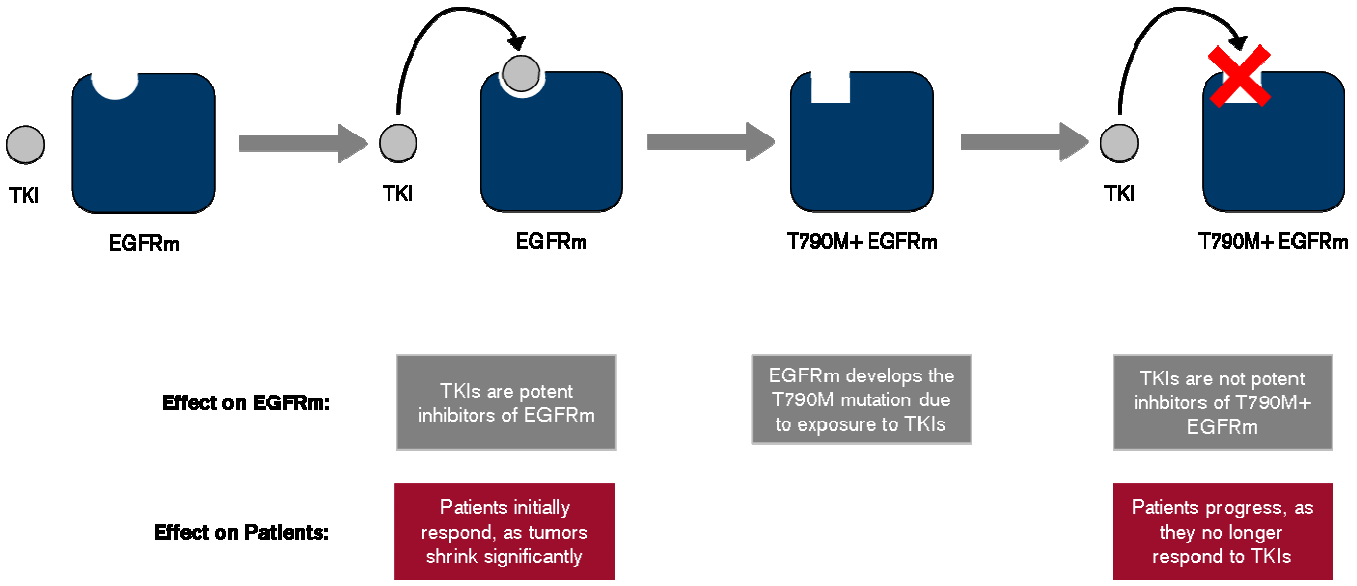
Studies had suggested that the primary driver in efficacy for TKIs was a subpopulation of patients with NSCLC who responded favorably to treatment with TKIs. The common trait among all patients in this subpopulation was the L858R mutation in their EGFRs. This mutation activated EGFR (EGFRm), making it more susceptible to inhibition by TKIs. Over the years, additional studies confirmed this observation. In fact, Roche recently expanded the label of Tarceva to include first-line treatment of patients with locally advanced or metastatic EGFRm+ NSCLC following results from the EURTAC Phase III clinical trial. It is estimated that *ca*10-15% of Caucasians and *ca*30-35% of Asians are EGFRm+. While the label for Tarceva in the U.S. was not altered, various treatment guidelines have recommended testing patients for EGFRm+ NSCLC prior to administration of Tarceva. However, both Tarceva and Iressa have significant side-effect issues (namely skin-rash and diarrhea) that are related to the inhibition of wild-type (normal) EGFR.

## Development of Resistance

... around 50% of acquired resistance to Tarceva and Iressa are due to the T790M mutation

The development of resistance to TKIs is primarily driven by the emergence of the T790M "gatekeeper" mutation in EGFRm+. Patients with EGFRm+ NSCLC who are being treated with TKIs will eventually progress. These patients are no longer responsive to TKIs. It is estimated that *ca*50% of patients with EGFRm+ NSCLC who are taking TKIs progress due to the T790M mutation. Exhibit 23 shows how the mechanism for development of resistance to TKIs occurs.

Exhibit 23: **Mechanism for Development of Resistance to Tarceva / Iressa**




*Source: Clovis, Credit Suisse analysis*

## CO-1686

CO-1686 is an oral, irreversible inhibitor of primary and secondary mutant EGFRs in NSCLC. This compound potently inhibits EGFRm+ and T790M+ EGFRm+ by forming a covalent bond. Others drugs with mechanisms of action that involve formation of covalent bonds with their targets include Plavix, Nexium, and various penicillins. Clovis licensed the rights to CO-1686 from Avila Therapeutics in a deal with a potential total value of $290M. Avila Therapeutics is a private company that designs and develop covalent inhibitors using its Avilomics approach, combining wet chemistry, computational chemistry, and structural biology. The composition of matter patent for CO-1686 extends to 2028.

CO-1686 has the potential for the treatment of both first and second-line NSCLC patients and demonstrate less side effects than established TKI's

CO-1686 could potentially alter the landscape for treatment of EGFRm+ NSCLC. First, this compound could potentially fill the void in second-line treatment options for patients with EGFRm+ NSCLC who have failed treatment with Tarceva or Iressa. The T790M mutation accounts for *ca*50% of these patients. Second, CO-1686 could replace Tarceva as first-line treatment for patients with EGFRm+ NSCLC. CO-1686 was designed to potently inhibit both EGFRm and T790M EGFR. CO-1686 could be shown to be more efficacious than Tarceva. Third, CO-1686 improves on the safety profile of Tarceva and Iressa. This compound is about significantly more selective for EGFRm than normal EGFR. As a result, side effects such as skin rashes and diarrhea may reduce in severity for CO-1686 as compared to Tarceva or Iressa.

The lead indication of CO-1686 will likely be second-line treatment of EGFRm+ NSCLC, specifically of T790M+ NSCLC. In addition, CO-1686 could be developed as a first-line treatment in EGFRm+ NSCLC.

## Clinical Development Strategy

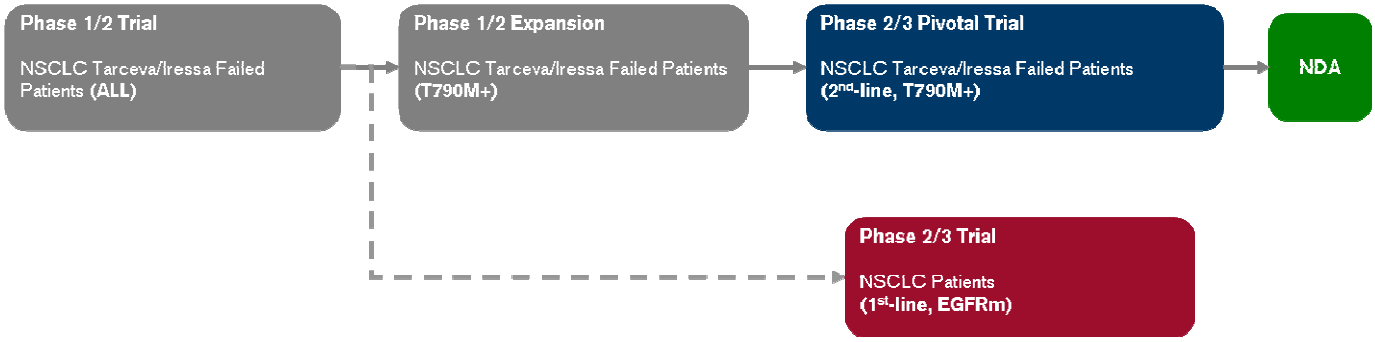
Clovis is planning an accelerated development pathway for CO-1686, with the potential for IND to NDA in ~4 years. Clovis will likely pursue second-line treatment of T790M+ NSCLC first, followed by first-line treatment in EGFRm+ NSCLC. The details of the clinical development plan for CO-1686 includes the following trials:

Clovis has an accelerated development pathway for CO-1686 – 2nd line NSCLC will be the first indication

- The Phase I/II trial is intended to show evidence of efficacy in patients with T790M+ NSCLC who failed Tarceva/Iressa. Clovis plans to enroll Tarceva/Iressa-failed patients with NSCLC regardless of mutational status. This trial will likely evaluate pharmacokinetics, safety, and tolerability of CO-1686 as well. Depending on the preliminary results, the Phase I/II trial could be expanded to include Tarceva/Iress-failed patients with T790M+ NSCLC. The intent behind the expansion study is to show proof-of-concept regarding efficacy of CO-1686 in this patient subpopulation. This trial could start in 2Q'12, with a potential data readout in 2H'13. This readout will be the key inflection point for CO-1686, demonstrating whether this compound actually works in patients with T790M+ NSCLC.
- The design of the Phase II/III pivotal trial will likely be based on the Phase I/II clinical results and dialogue with the FDA. This study will recruit Tarceva/Iressa-failed patients with T790M+ NSCLC. There is the potential to run a single arm, as there is no established second-line treatment in NSCLC. Clovis could initiate on this trial in 1H'14.
- Depending on the results of the Phase I/II trial, Clovis could concurrently launch a Phase II/III trial that compares CO-1686 to Tarceva in EGFRm+ NSCLC. This study will likely use progression-free survival, which may be acceptable to the FDA.

The planned development pathway for CO-1686 is illustrated in Exhibit 24.

**Exhibit 24: Proposed Development Pathway for CO-1686**




*Source: Clovis*

## Preclinical Studies

So far, CO-1686 has only been examined in preclincial studies. The basic chemical studies have shown that that CO-1686 is more selective (up to 200-fold) for EGFRm and T790M+ EGFRs relative to normal wild-type EGFR. Studies with animal models containing initially activating and T790M mutant EGFR have demonstrated dose response. Studies with mice suggest that CO-1686 does not target wild-type EGFR, as no loss of body weight was observed during CO-1686 administration. Clovis is currently still working on exploratory toxicology studies, with an intention to file an IND in 1Q'12.

CO-1686 is up to 200-fold more selective for EGFRm/ T790M+ EGFR than wild-type EGFR

## Companion Diagnostic

Like CO-101, Clovis plans to have a companion diagnostic on the market that enables physicians to identify patients with the T790M mutation. Clovis has partnered with Roche Molecular System to develop a PCR-based companion diagnostic for CO-1686 to test for the T790M mutation as well as other EGFR mutations for NSCLC. Clovis and Roche will likely first validate the test using tissue samples obtained from tumor biopsies. Afterwards,

Roche is developing a companion diagnostic to identify patients with the T790M mutation

Clovis will likely used to the test to prospectively identify patients for trials for CO-1686. The companion diagnostic will likely be approved concurrently with the CO-1686. Roche Molecular Systems will be responsible for commercializing the test globally.

## Competitive Landscape

The late- and mid-stage pipelines for NSCLC are presented in Exhibit 7 and Exhibit 8.

**Exhibit 25: Late-Stage Pipeline for NSCLC**

| Compound | Company | Phase | Route of Administration | Mechanism of Action |
|---|---|---|---|---|
| Abraxane | Celgene | NDA | Intravenous | Microtubules (Tubulin) |
| Erbitux | Eli Lilly | BLA | Intravenous | EGFR (Epidermal Growth Factor Receptor) |
| Afatinib | Boehringer Ingelheim | III | Oral | EGFR (Epidermal Growth Factor Receptor), HER2/neu or ErbB-2 |
| Dacomitinib | Pfizer | III | Oral | EGFR (Epidermal Growth Factor Receptor) |
| Iniparib | Sanofi | III | Intravenous | Poly ADP-Ribose Polymerase (PARP) |
| Lucanix | NovaRx | III | Intradermal | Immune System |
| MAGE-A3 ASCI | GSK | III | Intramuscular | Immune System |
| Necitumumab | Eli Lilly | III | Intravenous | EGFR (Epidermal Growth Factor Receptor) |
| Nexavar | Onyx | III | Oral | Platelet-derived growth factor receptor (PDGFR), Raf kinase, KIT/c-KIT, Tyrosine Kinases, RET, VEGF Receptor (VEGFR) |
| Ramucirumab | Eli Lilly | III | Intravenous | VEGF Receptor (VEGFR) |
| Stimuvax | Merck KGaA | III | Subcutaneous | Mucin 1 (MUC-1), Immune system |
| Talactoferrin | Agennix | III | Oral | Immune System |
| Tavocept | BioNumerik | III | Intravenous | Reactive Oxygen Species/Free Radicals |
| Tivantinib | ArQule | III | Oral | Hepatocyte growth factor receptor (c-Met) |
| Vargatef | Boehringer Ingelheim | III | Oral | VEGF Receptor (VEGFR), Platelet-derived growth factor receptor (PDGFR), Fibroblast Growth Factor Receptor (FGFR), Src Kinase Family |
| Yervoy | Bristol-Myers Squibb | III | Intravenous | Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) |
| Bavituximab | Peregrine | IIb | Intravenous | Phosphatidylserine |
| Tamibarotene | CytRx | IIb | Oral | Retinoic acid receptor (RARs) |
| TG4010 | Transgene | IIb | Subcutaneous | Mucin 1 (MUC-1), IL-2 (Interleukin-2), Immune System |
| Ganetespib | Synta | II/III | Intravenous | Heat Shock Protein 90 (HSP90) |
| Votrient | GSK | II/III | Oral | Platelet-derived growth factor receptor (PDGFR), VEGF Receptor (VEGFR), KIT/c-KIT |

*Source: BioMedTracker, Credit Suisse analysis*

**Exhibit 26: Mid-Stage Pipeline for NSCLC**

| Compound | Company | Phase | Route of Administration | Mechanism of Action |
|---|---|---|---|---|
| Afinitor | Novartis | II | Oral | Mammalian Target of Rapamycin (mTOR) |
| AUY922 | Novartis | II | Intravenous | Heat Shock Protein 90 (HSP90) |
| Belinostat (IV) | Spectrum | II | Oral | Histone Deacetylase (HDAC) |
| BKM120 | Novartis | II | Oral | PI3K/AKT pathway |
| BMS-690514 | Bristol-Myers Squibb | II | Oral | VEGF Receptor (VEGFR), HER2/neu or ErbB-2 |
| BMS-844203 | Bristol-Myers Squibb | II | Intravenous | |
| Cabozantinib | Exelixis | II | Oral | RET, VEGF Receptor (VEGFR), KIT/c-KIT, Angiopoietin Receptors (TIE-1 and TIE-2), FMS-like tyrosine kinase 3 (FLT-3), Hepatocyte growth factor receptor (c-Met) |
| Cadi-05 | Cadila | II | Intradermal | Toll-Like Receptor 2 (TLR2) |
| Capoxigem | Tragara | II | Oral | Cyclooxygenases (COX-1, COX-2, and COX-3) |
| CBP501 | CanBas | II | Intravenous | Cyclin Dependent Kinase (CDK) |
| Cilengitide | Merck KGaA | II | Intravenous | Integrin Alpha-V Family |
| Cixutumumab | Eli Lilly | II | Oral | IGF-1R (Insulin-like Growth Factor-1 Receptor) |
| CRLX101 | Cerulean | II | Intravenous | Topoisomerase I (Topo-I), Hypoxia Inducible Factor-1 alpha (HIF-1a) |
| CS-7017 | Daiichi Sankyo | II | Oral | PPAR |
| Custirsen | Teva | II | Intravenous | Clusterin / Apolipoprotein J |
| EC145 | Endocyte | II | Intravenous | Microtubules (Tubulin) |
| Entinostat | Syndax | II | Oral | Histone Deacetylase (HDAC) |
| Farletuzumab | Eisai Co | II | Intravenous | Folate Receptor (FOLR1) |
| Halaven | Eisai | II | Intravenous | Microtubules (Tubulin) |
| HyperAcute | NewLink Genetics | II | Intradermal | Irradiated Cancer Cell-Based Immunotherapy |
| Imetelstat | Geron | II | Intravenous | Telomerase |
| Imprime PGG | Biothera | II | Intravenous | Complement Proteins, Immune system |
| Inlyta | Pfizer | II | Oral | VEGF (Vascular endothelial growth factor), Platelet-derived growth factor (PDGF) |
| IPI-504 | Infinity | II | Intravenous | Heat Shock Protein 90 (HSP90) |
| ISIS-EIF4ERx | Isis | II | Intravenous | Eukaryotic translation initiation factor 4E (eIF4E) |
| Ixempra | Bristol-Myers Squibb | II | Intravenous | Microtubules (Tubulin) |
| Linifanib | Abbott | II | Oral | VEGF (Vascular endothelial growth factor), Platelet-derived growth factor (PDGF), FMS-like tyrosine kinase 3 (FLT-3), KIT/c-KIT |
| LY2181308 | Eli Lilly | II | Intravenous | Survivin |
| LY2523355 | Eli Lilly | II | Intravenous | Kinesin spindle protein (KSP) |
| LY2603618 | Eli Lilly | II | Intravenous | Cell Cycle Checkpoint Kinase 1 (Chk1) |
| LY3012207 | Eli Lilly | II | Intravenous | Platelet-derived growth factor receptor (PDGFR) |
| Mapatumumab | HGS | II | Intravenous | TRAIL-R1 |
| MEDI-575 | AstraZeneca | II | Intravenous | Platelet-derived growth factor alpha (PDGFa) |
| MetMAb | Roche | II | Intravenous | Hepatocyte growth factor receptor (c-Met) |
| MK-0646 | Merck | II | Intravenous | IGF-1R (Insulin-like Growth Factor-1 Receptor) |
| MK-2206 | Merck | II | Oral | PI3K/AKT pathway |
| NGR-hTNF | MolMed | II | Intravenous | Tumor Necrosis Factor-alpha (TNF-alpha),TNFR:Fc |
| Ombrabulin | Sanofi | II | Intravenous | Microtubules (Tubulin) |
| OSI-906 | Astellas | II | Oral | IGF-1R (Insulin-like Growth Factor-1 Receptor) |
| Reolysin | Oncolytics | II | Intravenous | Ras |
| RG7414 | Roche | II | Intravenous | EGFL7 |
| Sapacitabine | Cyclacel | II | Oral | DNA synthesis |
| Selumetinib | AstraZeneca | II | Oral | Mitogen-activated ERK kinase (MEK) |
| Tigatuzumab | Daiichi Sankyo | II | Intravenous | TRAIL-R2 (KILLER/DR5) |
| Volasertib | Boehringer Ingelheim | II | Oral | Polo-like kinase 1 (Plk1) |
| Zolinza | Merck & Co., Inc. | II | Oral | Histone Deacetylase (HDAC) |
| Zortress | Novartis AG | II | Oral | Mammalian Target of Rapamycin (mTOR) |

*Source: BioMedTracker, Credit Suisse analysis*

# CO-338

## Importance of BRCA for PARP inhibitors

Poly-ADP ribose protein (PARP) inhibitors have garnered significant attention due to their abilities to enhance the effects of radiation therapy or cytotoxic chemotherapy, as well as potentially exploiting certain cancers inherent molecular defects .

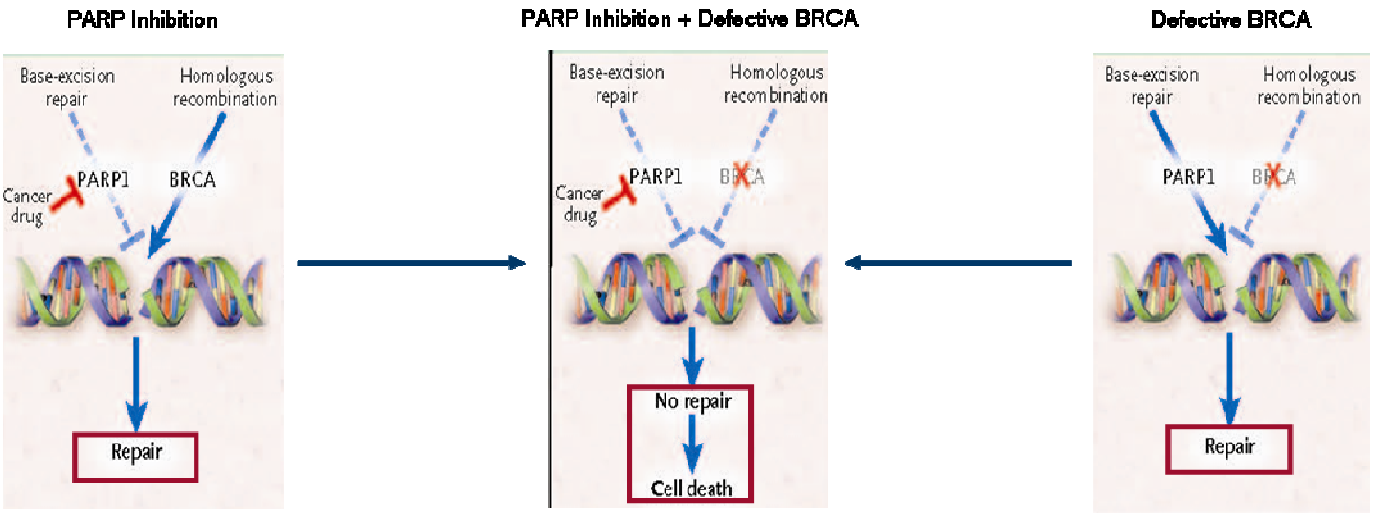
PARP inhibitors are arguably one of the most exciting classes of new oncology drugs

There are two types of PARP, PARP-1 and PARP-2. Both are involved in pathways that signal DNA repair. Studies have shown that the loss of both PARPs can cause cell death by limiting repair of damaged DNA. So far, clinical trials have demonstrated that PARP inhibitors do have anti-cancer activity, but will likely only work in select patient populations.

Studies have suggested that patients with defective BRCAs may respond more favorably to PARP inhibitors. The reasoning behind this observation is that pathways associated with BRCAs are involved DNA repair. There are two types of BRCA – BRCA1 and BRCA2. Defective BRCAs cause cell death by preventing the repair of damaged double –stranded DNA. Inhibition of PARP-1 leads to the failure of to repair single stranded DNA breaks – and eventually cause double stranded DNA breaks (via collapse of the replication fork). Thus patients with defective BRCAs could respond more favorably to PARP inhibitors, as both pathways associated with DNA repair are shut down.

PARP is involved in DNA repair, inhibition of which in certain cells/combinations (particularly BRCA defective) may results in cell death

**Exhibit 27: Effect of PARP Inhibition and Defective BRCA on Cell Death**




*Source: Clovis*

## CO-338

CO-338 (aka PF-01367338, AG-014699) is an oral, small molecule inhibitor of PARP. Clovis licensed exclusive global rights to develop and commercialize CO-338 from Pfizer in June 2011. Clovis made an upfront payment to Pfizer by issuing a 5% convertible note with a $7.0M principal amount. The total possible value of this deal is $170M. Clovis will likely target germline BRCA-mutant breast cancer and serous BRCA-mutant ovarian cancer as initial indications for CO-338. Obtaining intellectual property protection could be difficult, so protection around CO-338 will likely come from orphan drug designation.

## Clinical studies to-date

Clovis has conducted Phase I and II studies evaluating the IV formulation of CO-338 in patients with solid tumors.

- The first Phase I trial was focused on finding the most pharmacologically active and safest dose of the IV formulation of CO-338 as well as the optimal dose of temozolomide (TMZ) to be sued with CO-338. This study found that the recommended doses for CO-338 and TMZ are 12 $mg/m^2$ and 200 $mg/m^2$ respectively.
- In addition, Clovis has conducted a Phase II trial that evaluated CO-338 in combination with TMZ in metastatic melanoma. In this study, 46 patients with metastatic melanoma were treated with 12 $mg/m^2$ of CO-338 per day for three cycles followed by 200 $mg/m^2$ of TMZ every 21 days. Clovis reported that 17% of patients had partial responses and another 17% of patients had stable disease for up to 24 weeks. The median overall survival was 9.9 months. The common adverse events associated with this combination treatment regimen were gastrointestinal side effects including nausea and vomiting.

## On-going clinical studies

CO-338 is currently being studied in a few on-going and planned clinical trials.

- Clovis is conducting a Phase I, dose escalation trial evaluating the IV formulation of CO-338 with other chemotherapies including carboplatin, carboplatin + paclitaxel, cisplatin + Alimta, and epirubicin + cyclophosphamide. This trial recruited patients with solid tumors. As of October 2011, 52 patients had been enrolled and the maximum tolerated dose had not been reached yet. Some responses have been observed in the 27 evaluable patients; three patients (2 BRCA-mutant breast cancer and 1 BRCA-mutant ovarian cancer) had partial responses to CO-338. This study was recently amended to include an arm to evaluate an oral formulation of CO-338 in combination with cisplatin.
- The IV formulation of CO-338 is also being evaluated in 2 investigator-sponsored trials. The first is a Phase I/II trial evaluating CO-338 in germline BRCA-mutant breast and ovarian cancer. The second is a Phase II trial evaluating CO-338 as an adjuvant treatment in patients with high risk germline BRCA-defective breast cancer and triple negative breast cancer.
- Clovis will likely conduct a Phase I trial to determine the continuous dosing schedule for CO-338. This study will likely recruit ~30 patients with BRCA deficiencies.
- Pending the results from the Phase I studies, Clovis could potentially initiate Phase III studies in germline BRCA-mutant metastatic breast cancer and serous BRCA-mutant ovarian cancer in 2013.

## Disappointing recent PARP programs

There have been some recent high-profile failures in the clinical development of PARP inhibitors. These failures have highlighted the importance of identifying the “right” patients who will likely benefit from treatment with PARP inhibitors.

- In January 2011, Sanofi announced the failure of its Phase III trial evaluating iniparib, a PARP inhibitor, used in combination with gemcitabine and paclitaxel in triple-negative breast cancer. The study failed to meet primary endpoints of overall survival and progression-free survival. For this trial, Sanofi did not assess the molecular signatures (e.g. BRCA 1/2) of patients’ tumors. In June 2011,

Sanofi began to analyze the Phase III data to determine if patients with certain molecular subtypes of triple-negative breast cancer may respond more favorably to iniparib. Based on the results from this study, Sanofi could initiate another Phase III trial in a patient population that will likely have the best responses to iniparib.

- In February 2011, AstraZeneca canceled its plans to evaluate olaparib as a potential treatment of BRCA1/2+ breast cancer in a Phase III study. The decision to cancel further development was triggered by concerns regarding efficacy of olparib. First, results from a Phase II study suggesting that olarparib was not effective in treating in patients with BRCA1/2+ ovarian cancer. Second, the multi-tablet regimen potentially caused toxicity issues in patients.

- In December 2011, AstraZeneca announced its decision to discontinue clinical development of olaparib as a potential maintenance treatment of serous ovarian cancer. An interim analysis of data from an on-going Phase II trial for olaparib suggested that the positive effect on progression-free survival would likely not lead to an overall survival benefit. In addition, AstraZeneca was unable to find a proper tablet dose for use in Phase III studies. This Phase II trial evaluated olaparib in patients with serous ovarian cancer who had responded to previous platinum-containing therapy.

Clovis will likely benefit from failures of iniparib and olaparib, the leading PARP inhibitors in the clinical development pipeline due to the decrease in competition with CO-338.

# Financials and Valuation

Our $21 TP is based on a company DCF, only assuming CO-101 revenues

Common to our financial modeling and valuation of small- and mid-cap biotech companies in our coverage universe, we model the financials and valuations based solely on the development of the lead project, in this case CO-101 (for which we have previously outlined our revenue in this report). We model the medium-to-long-term cost basis for Clovis to reflect development and commercial support of CO-101 only, with no significant additional investment in future products (i.e. Our long-term R&D and SG&A costs move to 5% and 15% of revenue respectively). Our DCF simply discounts the company's cash flows through 2021 with no terminal value. The biggest sensitivity (outside revenues assumptions) to our valuation is the risk-weighting (of approval) we apply to CO-101. Our target price conservatively assumes a 50% probability of success. A 100% probability of success yields a valuation of $39 per share (See Exhibit 28). The current *ca*$14 per share stock price implies a *ca*30% probability of success for CO-101. We estimate Clovis will have *ca*$2.70 cash/share by the end of 2012. Finally, we emphasize that our valuation methodology does not take into account the various upside scenarios, which include (1) greater penetration of CO-101 into locally advanced and metastatic pancreatic cancer (first-line, hENT1-high patients) and (2) values for CO-1686 and CO-338.

**Exhibit 28: DCF Valuation for Clovis at 100% Probability of Success**

| Discount Rate / Probability of CO101 success | 5% | 7.5% | 10% | 12.5% | 15% |
|---|---|---|---|---|---|
| **10%** | $7.71 | $7.00 | $6.40 | $5.90 | $5.47 |
| **30%** | $17.46 | $15.33 | $13.54 | $12.03 | $10.74 |
| **50%** | $27.21 | $23.66 | **$20.68** | $18.15 | $16.00 |
| **70%** | $36.95 | $32.00 | $27.82 | $24.28 | $21.27 |
| **100%** | $51.58 | $44.49 | $38.52 | $33.47 | $29.17 |

*Source: Credit Suisse estimates*

The $21 TP is derived using our standard DCF methodology for valuing early development-stage biotechnology companies. We expect that CO-101 will likely be used in patients with hENT1-low locally advanced and metastatic pancreatic cancers. Our model assumes that CO-101 will launch in the U.S. and EU in Q1 2014 and remain under patent protection until 2021.(We see upside potential to both of these assumptions.) Our model assumes that CO-101 will reach worldwide peak revenues of *ca*$645M at an average price per patient (across the U.S. and EU) of *ca*$28K in 2021. We model revenues for CO-101 coming from the U.S. and major EU countries only. We risk-weight the cash flows with a 50% probability of success for CO-101, and employ a standard 10% discount rate. We assume zero cash flows beyond 2021. Working backwards from the current stock price, a *ca*30% probability of success would yield a *ca*$14 stock price. Our assumptions also include a further $150M equity raise in 2013. Our TP is based on the approval and launch of CO-101 in the U.S. and EU. If these events do not occur, there could be a material negative impact on our TP.

As shown in Exhibit 29 below, Clovis trades at a discount to the mean and median market capitalization and enterprise value of other companies with Phase III oncology drugs.

**Exhibit 29: Market Capitalization and EV of Companies Comparable to Clovis**

| Company | Ticker | Price | Market Capitalization | EV |
|---|---|---|---|---|
| Clovis | CLVS | $14.03 | $302.9 | $151.9 |
| Pharmacyclics | PCYC | $14.99 | $1,026.2 | $921.0 |
| AVEO Pharmaceuticals | AVEO | $14.19 | $594.9 | $359.1 |
| Micromet | MITI | $7.37 | $682.8 | $499.7 |
| Medivation | MDVN | $45.84 | $1,619.4 | $1,456.1 |
| Ziopharm Oncology | ZIOP | $4.21 | $292.8 | $173.9 |
| Oncothyreon | ONTY | $7.32 | $333.2 | $278.6 |
| Arqule | ARQL | $5.53 | $307.8 | $203.6 |
| | MEAN | | $693.8 | $556.0 |
| | MEDIAN | | $594.9 | $359.10 |

*Source: FactSet, Credit Suisse analysis*

**Exhibit 30: Clovis P&L Summary**

| (Dollars in thousands, except share and per share amounts) | 2011E | 2012E | 2013E | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E | 2020E | 2021E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CO-101 | 0 | 0 | 0 | 97,015 | 182,835 | 273,749 | 369,989 | 471,791 | 565,511 | 615,339 | 643,752 |
| **Revenues:** | **0** | **0** | **0** | **97,015** | **182,835** | **273,749** | **369,989** | **471,791** | **565,511** | **615,339** | **643,752** |
| **COGS** | **0** | **0** | **0** | **9,702** | **18,283** | **27,375** | **36,999** | **47,179** | **56,551** | **61,534** | **64,375** |
| **Gross Profit** | **0** | **0** | **0** | **87,314** | **164,551** | **246,375** | **332,990** | **424,612** | **508,960** | **553,805** | **579,377** |
| **Operating expenses:** | | | | | | | | | | | |
| Research and Development | 36,000 | 53,547 | 60,000 | 65,000 | 45,000 | 41,062 | 36,999 | 37,743 | 33,931 | 30,767 | 32,188 |
| Selling, General, and Administrative | 7,500 | 29,494 | 33,500 | 82,463 | 87,761 | 90,337 | 92,497 | 94,358 | 96,137 | 98,454 | 90,125 |
| Acquired IPRD | 7,000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total Operating Expenses** | **50,500** | **83,040** | **93,500** | **147,463** | **132,761** | **131,400** | **129,496** | **132,101** | **130,068** | **129,221** | **122,313** |
| **Operating Income (Loss)** | **(50,500)** | **(83,040)** | **(93,500)** | **(60,149)** | **31,791** | **114,975** | **203,494** | **292,510** | **378,893** | **424,584** | **457,064** |
| **Net Investment and Interest Income/(Expense)** | **1,529** | **745** | **1,032** | **444** | **478** | **1,300** | **3,230** | **5,580** | **8,635** | **12,071** | **15,765** |
| **Pretax Income (Loss)** | **(48,971)** | **(82,295)** | **(92,468)** | **(59,705)** | **32,269** | **116,275** | **206,724** | **298,090** | **387,528** | **436,655** | **472,829** |
| Provision For Income Taxes | 0 | 0 | 0 | 0 | 0 | 0 | (28,941) | (59,618) | (77,506) | (87,331) | (94,566) |
| *Effective Tax Rate* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *14%* | *20%* | *20%* | *20%* | *20%* |
| **Net Income (Loss)** | **(48,971)** | **(82,295)** | **(92,468)** | **(59,705)** | **32,269** | **116,275** | **177,782** | **238,472** | **310,022** | **349,324** | **378,263** |
| **Basic EPS** | **($2.26)** | **($3.79)** | **($3.48)** | **($1.90)** | **$1.02** | **$3.66** | **$5.57** | **$7.42** | **$9.56** | **$10.66** | **$11.41** |
| **Diluted EPS** | **($2.16)** | **($3.63)** | **($3.36)** | **($1.83)** | **$0.98** | **$3.47** | **$5.22** | **$6.87** | **$8.72** | **$9.55** | **$10.00** |
| Basic Shares Outstanding | 21,664 | 21,701 | 26,582 | 31,481 | 31,604 | 31,753 | 31,936 | 32,158 | 32,430 | 32,761 | 33,165 |
| Diluted Shares Outstanding | 22,664 | 22,702 | 27,531 | 32,639 | 33,017 | 33,477 | 34,039 | 34,724 | 35,560 | 36,580 | 37,824 |

*Source: Clovis, Credit Suisse estimates*

**Exhibit 31: Clovis Balance Sheet**

| *(Dollars in thousands)* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2011E** | **2012E** | **2013E** | **2014E** | **2015E** | **2016E** | **2017E** | **2018E** | **2019E** | **2020E** | **2021E** |
| Current Assets | | | | | | | | | | | |
| Cash and Cash Equivalents | 134,797 | 61,623 | 115,547 | 62,064 | 97,182 | 215,848 | 397,238 | 639,432 | 954,096 | 1,308,598 | 1,692,362 |
| Available for Sale Securities | 2,036 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Prepaid R&D Expenses | 4,320 | 6,426 | 10,800 | 9,750 | 5,400 | 4,106 | 3,700 | 4,152 | 3,732 | 3,692 | 4,184 |
| Other Current Assets | 3,030 | 4,982 | 5,610 | 8,848 | 7,966 | 7,884 | 7,770 | 7,926 | 7,804 | 7,753 | 7,339 |
| **Total Current Assets** | **144,183** | **73,031** | **131,957** | **80,662** | **110,548** | **227,838** | **408,708** | **651,510** | **965,632** | **1,320,043** | **1,703,885** |
| Property & Equipment, Net | 1,684 | 2,042 | 2,377 | 2,690 | 2,982 | 3,256 | 3,442 | 3,569 | 3,664 | 3,613 | 3,565 |
| Other Assets | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| **Total Assets** | **145,894** | **75,101** | **134,362** | **83,380** | **113,558** | **231,122** | **412,177** | **655,106** | **969,324** | **1,323,684** | **1,707,478** |
| Accounts Payable | 5,050 | 9,965 | 9,350 | 13,272 | 10,621 | 9,198 | 9,065 | 9,247 | 9,105 | 9,045 | 8,562 |
| Accrued R&D | 3,240 | 6,426 | 5,400 | 5,200 | 3,150 | 2,464 | 2,220 | 2,265 | 2,036 | 1,846 | 1,931 |
| Other Accrued Expenses | 1,010 | 2,491 | 2,805 | 4,424 | 3,983 | 3,942 | 3,885 | 3,963 | 3,902 | 3,877 | 3,669 |
| **Total Current Liabilities** | **9,300** | **18,882** | **17,555** | **22,896** | **17,754** | **15,604** | **15,170** | **15,475** | **15,043** | **14,768** | **14,163** |
| Non Current Liabilities | 115 | 115 | 115 | 115 | 115 | 115 | 115 | 115 | 115 | 115 | 115 |
| **Total Liabilities** | **9,415** | **18,997** | **17,670** | **23,011** | **17,869** | **15,719** | **15,285** | **15,590** | **15,158** | **14,883** | **14,278** |
| Common Stock | 23 | 24 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 |
| Additional Paid-in-Capital | 233,308 | 235,234 | 388,279 | 391,661 | 394,712 | 398,150 | 401,856 | 406,006 | 410,633 | 415,943 | 422,078 |
| Accumulated & Other Comprehensive Income | 48 | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 |
| Income/(Deficit) Accumulated During Development Stage | (96,900) | (179,195) | (271,663) | (331,369) | (299,100) | (182,825) | (5,043) | 233,429 | 543,452 | 892,775 | 1,271,039 |
| **Total Shareholders Equity** | **136,479** | **56,104** | **116,692** | **60,369** | **95,690** | **215,404** | **396,893** | **639,517** | **954,166** | **1,308,801** | **1,693,200** |
| **Total Liabilities & Shareholders Equity** | **145,894** | **75,101** | **134,362** | **83,380** | **113,558** | **231,122** | **412,177** | **655,106** | **969,324** | **1,323,684** | **1,707,478** |

*Source: Clovis, Credit Suisse estimates*

**Exhibit 32: Clovis Cash Flow Statement**

| *(Dollars in thousands)* | 2011E | 2012E | 2013E | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E | 2020E | 2021E |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Net Income / (Loss) | (48,971) | (82,295) | (92,468) | (59,705) | 32,269 | 116,275 | 177,782 | 238,472 | 310,022 | 349,324 | 378,263 |
| Depreciation | 117 | 142 | 165 | 187 | 207 | 226 | 239 | 248 | 255 | 251 | 248 |
| Share-Based Compensation | 870 | 1,661 | 2,691 | 2,906 | 2,412 | 2,581 | 2,555 | 2,606 | 2,554 | 2,528 | 2,402 |
| Amortization of Premiums and Discounts for Sale Securities | 121 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gain on Sale of Available Securities | (16) | (6) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Non-Cash Acquired IPRD | 7,000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Changes in Operating Assets and Liabilities: | | | | | | | | | | | |
| Prepaid and Accrued R&D Expenses | (2,449) | 1,080 | (5,400) | 850 | 2,300 | 608 | 163 | (407) | 191 | (149) | (407) |
| Other Operating Assets | (1,934) | (1,952) | (628) | (3,238) | 882 | 82 | 114 | (156) | 122 | 51 | 414 |
| Accounts Payable | 3,650 | 4,915 | (615) | 3,922 | (2,651) | (1,423) | (133) | 182 | (142) | (59) | (484) |
| Other Accured Expenses | 270 | 1,481 | 314 | 1,619 | (441) | (41) | (57) | 78 | (61) | (25) | (207) |
| **Net Cash from Operating** | **(41,342)** | **(74,975)** | **(95,941)** | **(53,460)** | **34,978** | **118,307** | **180,663** | **241,023** | **312,940** | **351,920** | **380,229** |
| Investing Activities | | | | | | | | | | | |
| Purchase of P&E | (850) | (500) | (500) | (500) | (500) | (500) | (425) | (375) | (350) | (200) | (200) |
| Sale/(Purchase) of Available Securities | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Maturities and Sales of Available for Sale Securities | 9,614 | 2,036 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Net Cash from Investing** | **8,764** | **1,536** | **(500)** | **(500)** | **(500)** | **(500)** | **(425)** | **(375)** | **(350)** | **(200)** | **(200)** |
| Proceeds from Convertible Preferred & Common Stock | 129,363 | 0 | 150,000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Accumulated Issuance Costs of Planned IPO | (1,514) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Proceeds from Stock Option Exercises | 1,072 | 265 | 365 | 477 | 640 | 859 | 1,152 | 1,546 | 2,074 | 2,783 | 3,734 |
| Proceeds from Issuance of Convertible Promissory Notes, Net of Issuance Costs | 27,903 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Net Cash from Financing** | **156,824** | **265** | **150,365** | **477** | **640** | **859** | **1,152** | **1,546** | **2,074** | **2,783** | **3,734** |
| Effect of Exchange Rate Changes on Cash and Cash Equivalents | 39 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Change in Cash Equivalents** | **124,286** | **(73,174)** | **53,924** | **(53,483)** | **35,118** | **118,666** | **181,390** | **242,194** | **314,664** | **354,503** | **383,764** |

*Source: Clovis, Credit Suisse estimates*

# Risks to our valuation

Key risks to our Clovis target price include the following:

- **CO-101 approval.** Our model assumes that CO-101 will be approved and launched in both the U.S. and EU in Q1 2014. If one or the other of these events do not occur, then there would be a material negative effect on the stock price.
- **Readout from LEAP trial.** Our model assumptions are based on expectations that CO-101 will show a statistically significant survival benefit relative to gemcitabine in hENT1-low patients with metastatic pancreatic cancer. If CO-101 is shown to be equally or less efficacious than gemcitabine in prolonging survival in this patient subpopulation, then CO-101 may not be approved or sales of CO-101 may fall short of expectations.
- **Financing risk.** Clovis recently raised net proceeds of $130M in an IPO in November 2011. We expect Clovis will be able to fund operations into early 2013. We are modeling a capital raise (and associated dilution) of $150M in 2013 to fund commercialization of CO-101 in the U.S. and EU. The need for additional capital and/or more than expected dilution would have a negative impact on our valuation.
- **CO-101 launch and sales ramp.** In modeling CO-101, we developed a patient-driven model to attempt to forecast the launch trajectory and peak sales. However, if any of the following parameters are worse than our expectations, our sales estimates for CO-101 could be too high:
    - Pricing
    - Clovis economics
    - Treatment rate
    - Average duration of therapy
    - Emergence of new competing agents

# Management

Of the five members of Clovis' management team, four were former executives of Pharmion Corporation, which was acquired by Celgene in 2008 for $2.9B. All five executives have significant experience obtained from leading and managing operations at small biotechnology companies and divisions of large biotechnology and pharmaceutical companies. Management includes:

- **Patrick J. Mahaffy, President & CEO:** Mr. Mahaffy is one of the co-founders of Clovis. He has served as President and CEO of Clovis since inception of the company in April 2009. Previously, Mr. Mahaffy had served as President and CEO at three biotech companies: Pharmion (2000-2008), NeXagen (1992-1998), and NeXstar (1992-1999). Prior to leading biotech companies, Mr. Mahaffy was a Vice President at E.M. Warburg Pincus and Company. Mr. Mahaffy currently serves on the Board of Directors of Orexigen Therapeutics and Flexion Therapeutics.

- **Andrew R. Allen, BM, BCh, MA, MRCP, PhD, EVP of Clinical & Pre-Clinical Development & CMO:** Dr. Allen is one of the co-founders of Clovis. He has served as Executive Vice President of Clinical and Pre-Clinical Development and CMO since Clovis was founded in April 2009. Dr. Allen had served in the same role at Pharmion (2006-2008). Prior to Pharmion, he was Vice President of BioPharma Development and Head of the Oncology Therapeutic Unit at Chiron Corporation. Dr. Allen has also served as a global project head of the oncology franchise at Abbott Laboratories and various positions at McKinsey & Company. Dr. Allen currently serves on the Board of Directors at Nodality, Inc.

- **Steven L. Hoerter, SVP, Commercial Operations:** Mr. Hoerter joined Clovis in August 2011. Prior to Clovis, Mr. Hoerter served as General Manager and Management Center Head at F. Hoffmann-La Roche Ltd. For the Sub-Saharan Africa and Indian Ocean Region. Mr. Hoerter has also held a variety of positions at Genentech, including a senior leadership position in the BioOncology business. Previously, Mr. Hoerter served in various roles at Chiron Corporation and Eli Lilly.

- **Gillian C. Ivers-Read, EVP, Technical Operations and Chief Regulatory Officer:** Ms. Ivers-Read is one of the co-founders of Clovis and has served in this role since inception of Clovis in April 2009. Prior to Clovis, Ms. Ivers-Read served as EVP, Development Operations at Pharmion (2002-2008). Previously, she has held various positions at Hoechst Marion Roussel / Aventis (1996-2001), Argus (1994-1996), and Marion Merrell Dow (1984-1994).

- **Erle T. Mast, EVP & CFO:** Mr. Mast is one of the co-founders of Clovis and has served as EVP and CFO since the founding of Clovis in April 2009. Mr. Mast served in the same capacity at Pharmion Corporation from 2002 to 2008. Previously, Mr. Mast has worked at Dura Pharmaceuticals / Elan Corporation (1997-2002). He served as CFO of the Global Biopharmaceuticals business for Elan from 2000 to 2002. Prior to this, Mr. Mast was the VP of Finance at Dura Pharmaceuticals. Previously, Mr. Mast was Partner at Deloitte & Touche. He currently serves on the Board of Directors at Somaxon Pharmaceuticals and Zogenix Inc.

# Appendix

## Background to lung cancer – Relevant to CO-1686

As previously discussed previously, Clovis is developing CO-1686, a oral small molecule inhibitor of EGFR mutations for the treatment of NSCLC. The Phase I study is due to initiate in H1 2012. Clovis has an accelerated development goal that could take CO-1686 from IND to NDA in around 4 years. Below we briefly outline a background to lung cancer.

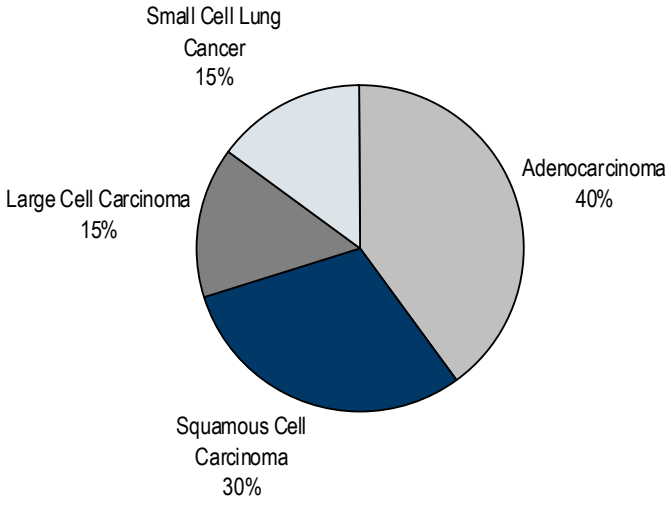
Of all cancers in the U.S. and EU, lung cancer is the leading cause of death, despite having the third highest incidence. In the U.S., there are *ca*221,000 new cases of lung cancer and *ca*221,000 deaths caused by lung cancer annually according to the American Cancer Society. In the EU, the European Cancer Observatory estimates that there *ca*288,000 new cases of lung cancer and *ca*288,000 deaths caused by lung cancer annually.

Lung cancer is typically classified as either “non-small cell” and “small cell”.

- Non-small cell lung cancer (NSCLC) accounts for *ca*85% of all lung cancers. NSCLC can be further categorized as adenocarcinoma, squamous cell carcinoma, or large cell carcinoma. Adenocarcinoma usually occurs in the bronchial mucosal glands, and represent *ca*40% of all lung cancers. Squamous cell carcinoma is generally found in the central parts of the lung, and accounts for *ca*30% of all lung cancers. Large cell carcinoma typically occurs in the outer parts of the lung, and represent *ca*15% of all lung cancers.
- Small cell lung cancer (SCLC) makes up the remaining *ca*15% of all lung cancers. SCLC generally grows and spreads faster than NSCLC. SCLC can be further characterized as pure small cell, mixed small cell, and combined small cell.

Exhibit 33 presents the distributions of these lung cancers.

**Exhibit 33: Distribution of Types of Lung Cancers**




*Source: Credit Suisse estimates*

The majority of patients with NSCLC are usually diagnosed at later stages, as symptoms are generally not seen at early stages. In the U.S., it is estimated that *ca*78% of all NSCLCs are diagnosed when the disease has become locally advanced or metastatic.

The five-year survival rate for NSCLC decreases from *ca*52% to *ca*4% as the disease at diagnosis moves from localized to metastatic. The percentage of and five-year survival for the three stages of NSCLC are presented in Exhibit 34.

**Exhibit 34: Disease Stage Distribution and Survival at Time of Diagnosis in the U.S.**

| Disease Stage | Patients at Diagnosis | Five-Year Relative Survival Rate |
|---|---|---|
| Metastatic | 56% | 4% |
| Locally Advanced | 22% | 24% |
| Localized | 15% | 52% |
| Unknown | 7% | 8% |

*Source: NCI SEER*

## Standard of care

The first-line standard of care varies depending on the stage of NSCLC. The various first-line treatment regimens for NSCLC is presented in Exhibit 35.

- The preferred treatment for patients with localized NSCLC is surgical removal of the tumor from the lungs followed by adjuvant chemotherapy. Most adjuvant treatment combination regimens are based on either carboplatin or cisplatin.
- The treatment of choice for patients with locally advanced NSCLC is combination chemotherapy regimens based on cisplatin or carboplatin.
- The treatment options for metastatic NSCLC varies depending on the type of NSCLC. For general NSCLC, the standard-of-care is combination chemotherapy based on either cisplatin or carboplatin. For NSCLC with non-squamous cell histology, treated brain metastases, and no history of hemoptysis, the use of combination chemotherapy based on Avastin is preferred. For NSCLC with non-squamous cell histology, Alimta is typically used in combination with cisplatin or carboplatin. For NSCLC with initial activating mutations (EGFRm+ NSCLC), Tarceva / Iressa monotherapy or combination chemotherapy based on either cisplatin or gemcitabine could be administered. For ALK+ NSCLC, patients will likely be treated with the recently approved Xalkori.

The standard of care for maintenance is similar across all stages of NSCLC, but varies depending on the type of NSCLC. The available treatment options for maintenance include docetaxel for general NSCLC, Alimta for NSCLC with non-squamous cell histology, and Tarceva or cisplatin-based combination chemotherapy for EGFRm+ NSCLC. Exhibit 35 lists the options available for maintenance in NSCLC.

The standard-of-care for second-line treatment of NSCLC is Tarceva / Iressa. This drug is usually given to patients with NSCLC who failed first-line treatments. Physicians will likely offer patients salvage therapy at this point as well. It is important to note that there is no established standard-of-care for patients who received Tarceva / Iressa.

Exhibit 35: **Standard of Care for NSCLC**

| Treatment Line | Localized NSCLC | Locally Advanced NSCLC | Metastatic NSCLC |
|---|---|---|---|
| **First-Line Treatment** | **General**<br>- Surgical Treatment<br><br>**Adjuvant Therapy**<br>- Cisplatin + Vinorelbine<br>- Cisplatin + Etoposide<br>- Cisplatin + Vinblastine<br>- Cisplatin + Gemcitabine<br>- Cisplatin + Docetaxel<br>- Cisplatin + Alimta<br>- Cisplatin + paclitaxel | **General**<br>- Cisplatin + Etoposide<br>- Cisplatin + Vinblastine<br>- Carboplatin + Paclitaxel<br>- Cisplatin + Vinblastine<br>- Carboplatin + Paclitaxel | **General**<br>- Cisplatin + Paclitaxel<br>- Cisplatin + Gemcitabine<br>- Cisplatin + Docetaxel<br>- Cisplatin + Vinorelbine<br>- Carboplatin + Paclitaxel<br>- Carboplatin + Docetaxel<br>- Carboplatin + Gemcitabine<br>- Carboplatin +Vinorelbine<br><br>**NSCLC with Non-Squamous Cell Histology, Treated Brain Metastases, and No History of Hemoptysis**<br>- Alimta + Paclitaxel + Avastin<br>- Cisplatin + Gemcitabine + Avastin<br>- Docetaxel + Avastin<br>- Alimta + Avastin<br><br>**NSCLC with Non-Squamous Cell Histology**<br>- Cisplatin + Alimta<br>- Carboplatin + Alimta<br><br>**NSCLC (EGFRm+)**<br>- Cisplatin + Vinorelbine + Erbitux<br>- Tarceva / Iressa<br>- Gemcitabine + Docetaxel<br>- Gemcitabine + Vinorelbine<br><br>**NSCLC (ALK+)**<br>- Xalkori |
| **Second-Line Treatment** | **General**<br>- Tarceva / Iressa<br>- Salvage Therapy | | |
| **Maintenance** | **General**<br>- Docetaxel<br><br>**NSCLC with Non-Squamous Cell Histology, Treated Brain Metastases, and No History of Hemoptysis**<br>- Carboplatin + Paclitaxel + Avastin<br><br>**NSCLC with Non-Squamous Cell Histology**<br>- Alimta<br><br>**NSCLC (EGFRm+)**<br>- Tarceva / Iressa<br>- Cisplatin + Vinorelbine + Erbitux | | |

*Source: Clovis, Credit Suisse analysis*

# Background on breast cancer – Relevant to CO-338

Invasive breast cancer is a fatal disease characterized by abnormal growth in tissues of the breast. This cancer predominantly affects women. In the U.S., ACS estimates that there are *ca*230,000 new cases of invasive breast cancer and *ca*40,000 deaths due to breast cancer annually. In the EU, ECO estimates that the annual incidence of invasive breast cancer is *ca*333,000 and the number of deaths caused by breast cancer is *ca*90,000.

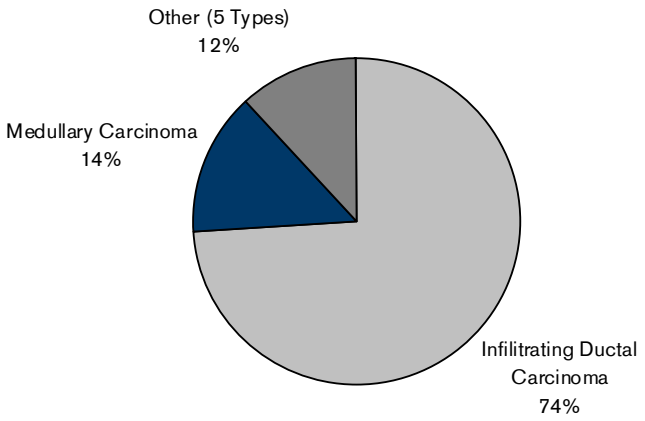
Invasive breast cancer can be classified by location and appearance of the tumors and the molecular signatures of the tumors.

- Invasive breast cancer can be described by one of seven types based on location and appearance of the tumors: 1) Ductal Carcinoma In-Situ; 2) Infilitrating Ductal

Carcinoma; 3) Medullary Carcinoma; 4) Infiltrating Lobular Carcinoma; 5) Tubular Carcinoma; 6) Mucinous Carcinoma; 7) Inflammatory Breast Cancer. The most prevalent type of is infilitrating ductal carcinoma, accounting for 78% of all invasive breast cancers. This type is characterized by lesions that look star-like or rounded on mammograms. Exhibit 36 provides descriptions and prevalences of the other types of invasive breast cancer.

- The molecular subtypes of invasive breast cancer are used in research settings primarily, but could become useful in planning treatments in the near future. There are four major molecular subtypes: 1) Luminal A; 2) Luminal B; 3) Triple Negative / Basal-Like; 4) HER2 type. The most prevalent molecular subtype is Luminal A, accounting for *ca*54% of all invasive breast cancers. This type of tumor tends to be ER+ and/or PR+, HER2-, and low Ki67. The descriptions and prevalences of other molecular subtypes are provided in Exhibit 37.

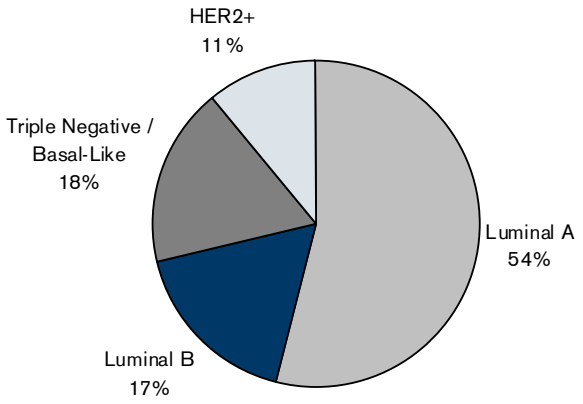
**Exhibit 36: Prevalence of Invasive Breast Cancer Types**




| Type | Description | Prevalence |
|---|---|---|
| Infiltrating Ductal Carcinoma | Lesions appear star-like or rounded on mammograms | ~74% |
| Medullary Carcinoma | Carcinoma cells resemble “gray matter” of the brain | ~14% |
| Infiltrating Lobular Carcinoma | Thickening occurs in upper-outer part of the breast | ~5% |
| Inflammatory Breast Cancer | Blockage occurs in lymph vessels and skin of the breast | ~3% |
| Tubular Carcinoma | Carcinoma cells have tubular structure under microscope | ~2% |
| Mucinous Carcinoma | Poorly defined carcinoma cells with mucus production | ~1% |
| Ductal Carcinoma In-Situ | Carcinoma cells found inside of ductal system | ~1% |

*Source: National Breast Cancer Organization*

**Exhibit 37: Prevalence of Invasive Breast Cancer Molecular Subtypes**

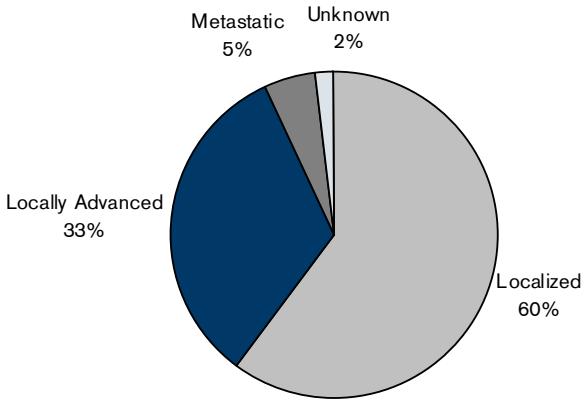



| Type | Description | Prevalence |
|---|---|---|
| Luminal A | ER+ and/or PR+, HER2-, Low Ki67 | ~54% |
| Triple Negative / Basal-Like | ER-, PR-, HER2-, Cytokerin 5/6+, and/or HER1+ | ~18% |
| Luminal B | ER+ and/or PR+, HER2+ (or HER2- and High Ki67) | ~17% |
| HER2+ | ER-, PR-, HER2+ | ~11% |

*Source: Susan G. Komen for the Cure*

Most patients with invasive breast cancer are diagnosed at the early stages of the disease. This trend has been primarily driven by the early screening programs for this cancer. The percentage of patients diagnosed at localized, locally advanced, and metastatic stages of invasive breast cancer are *ca*60%, *ca*33%, and *ca*5% respectively. The remaining *ca*2% of patients have unknown staging at the time of diagnosis. The five year relative survival rate is *ca*99% for localized, *ca*84% for locally advanced, and *ca*23% for metastatic. The distribution and survival rates for the various stages of breast cancer are presented in Exhibit 38.

**Exhibit 38: Distribution and Survival for Stages of Invasive Breast Cancer**



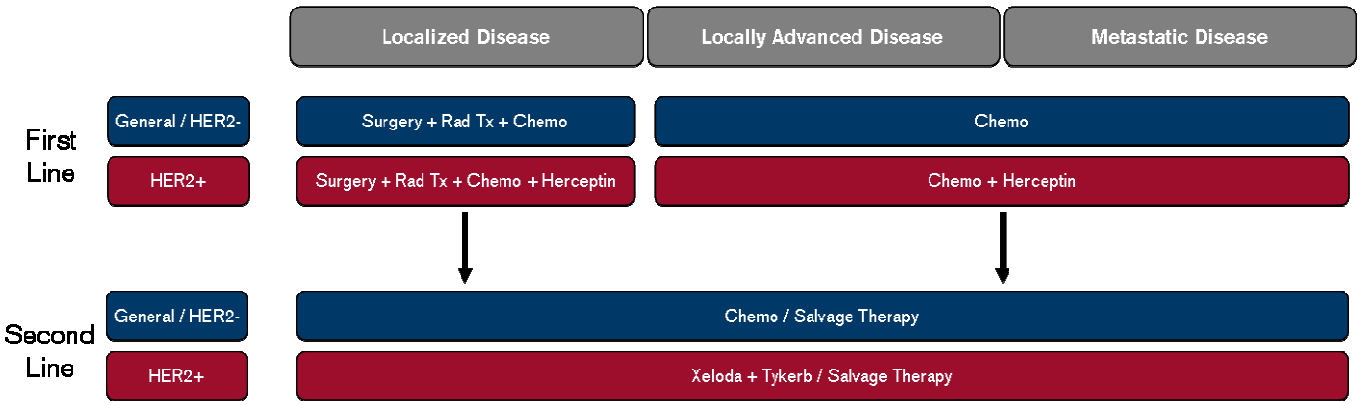

| Type | Stage Distribution | Five-Year Relative Survival Rate |
|---|---|---|
| Localized | 60% | ~99% |
| Locally Advanced | 33% | ~84% |
| Metastatic | 5% | ~23% |

*Source: NCI SEER*

## Standard-of-care for breast cancer

The current standard-of-care for breast cancer depends on the stage and HER2 status. For localized breast cancer, first-line treatment involves surgical treatment (lumpectomy or mastectomy), radiation therapy, and adjuvant chemotherapy. For locally advanced and metastatic breast cancer, first-line treatment is chemotherapy. Herceptin is usually added to treatment regimens to all stages of HER2+ breast cancer. The second-line treatment for all stages of breast cancer is chemotherapy. The combination of Xeloda and Tykerb are usually used in patients with HER2+ breast cancer. This treatment paradigm is illustrated in Exhibit 39.

**Exhibit 39: Current Standard-of-Care for Breast Cancer**

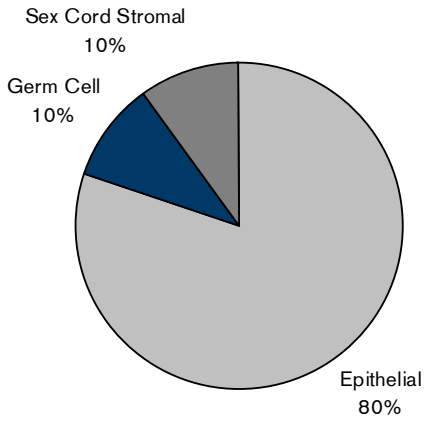



*Source: Credit Suisse research*

# Background to ovarian cancer – Relevant to CO-338

Ovarian cancer is a deadly disease with annual incidences of *ca*22,000 (ACS) and *ca*45,000 (ECO) in the U.S. and EU respectively. Ovarian cancers are typically classified according to the type of cell from which the tumors originated. Overall, there are >30 different types of ovarian cancer. The three main types of ovarian cancers are: 1) Epithelial; 2) Germ Cell; and 3) Sex Cord Stromal. The epithelial type occurs in cells lining the surface of the ovary, and account for *ca*80% of all ovarian cancers. Exhibit 40 provides descriptions and prevalences of the various types of ovarian cancer.

**Exhibit 40: Prevalence of Ovarian Cancer Types**

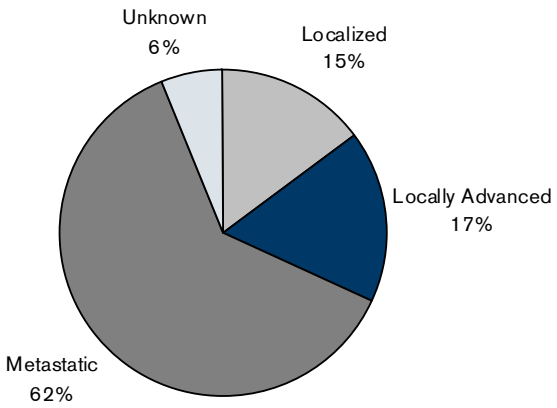



| Type | Description | Prevalence |
|---|---|---|
| Epithelial | Occurs in cells lining surface of ovary | ~80% |
| Germ Cell | Occurs in egg-producing cells in the ovary | ~10% |
| Sex Cord Stromal | Occurs in sex cords | ~10% |

*Source: JHMI, Credit Suisse estimates*

The majority of patients with ovarian cancer are diagnosed at later stages of the disease. Early diagnosis is usually difficult due to the lack of any obvious symptoms associated with ovarian cancer. The percentage of patients diagnosed at the localized, locally advanced, and metastatic stages are 15%, 17%, and 62% respectively. It is estimated the staging is unknown in *ca*7% of all patients with ovarian cancer. The five-year relative survival rate drops from *ca*93% for localized disease to *ca*27% for metastatic disease. The distribution and survival rates for the various stages of breast cancer are presented in .

**Exhibit 41: Distribution and Survival Statistics for Stages of Ovarian Cancer**



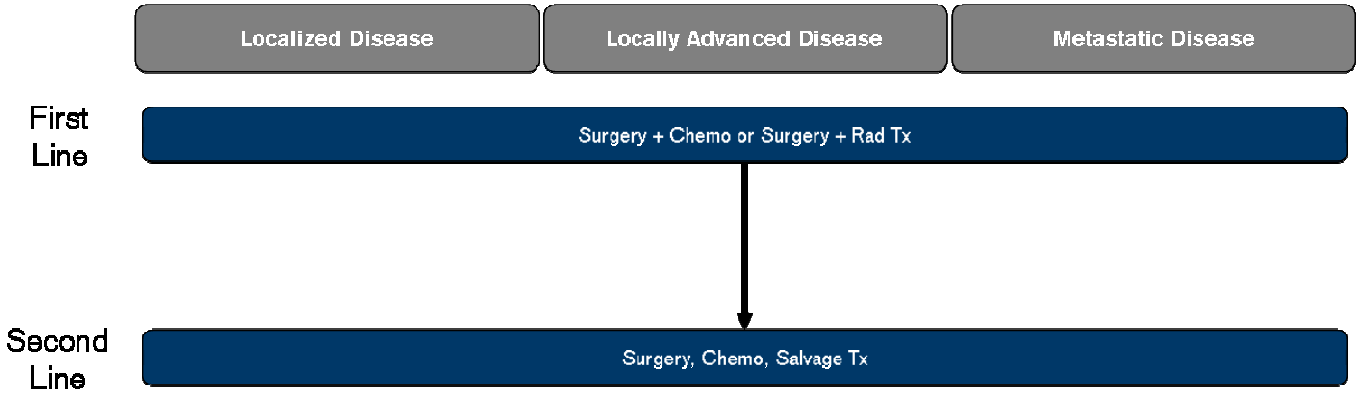

| Type | Stage Distribution | Five-Year Relative Survival Rate |
|---|---|---|
| Localized | 15% | ~93% |
| Locally Advanced | 17% | ~72% |
| Metastatic | 62% | ~27% |
| Unknown | 6% | ~22% |

*Source: NCI SEER*

## Current standard-of-care for ovarian cancer

The initial treatment for patients with ovarian cancer at all stages is surgical removal of the causative tumor. Afterwards, patients are usually treated with combination chemotherapy regimens. For patients with localized ovarian cancer, radiation therapy may considered instead of combination chemotherapy. For patients with recurrent ovarian cancer, the treatment options include surgical removal of any tumors or salvage therapy. This treatment paradigm is illustrated in Exhibit 42.

**Exhibit 42: Current Standard-of-Care for Breast Cancer**

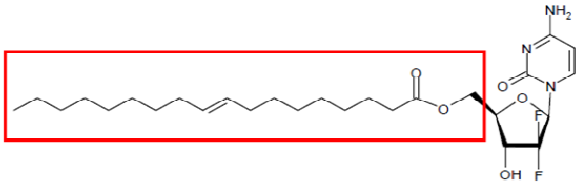



*Source: Credit Suisse research*

# CO-101 technology

Exhibit 43 describes the similarities and differences between CO-101 and gemcitabine:

**Exhibit 43: Comparison of CO-101 and Gemcitabine**

| | Gemcitabine | CO-101 |
|---|---|---|
| **Structure** |  ▪ Gemcitabine |  ▪ CO-101 consists of gemcitabine core with a long lipid side-chain |
| **Mechanism of Action** | ▪ Anti-cancer activity of gemcitabine is based on its ability to primarily target cells undergoing DNA synthesis.<br>▪ Gemcitabine is metabolized inside cells to active, phosphorylated forms, which then inhibit DNA synthesis. | ▪ Works in a similar fashion to gemcitabine. |
| **Mode of Entry** | • **Gemcitabine enters cancer cells primarily via the hENT1 membrane transporter.** | • **CO-101 can bypass the hENT1 membrane transporter and enter cancer cells directly, enabled by the long lipid side-chain** |

CO-101 has the same mechanism of action as Gemcitabine, but enters cancer cells independently of hENT1 membrane transporters

*Source: Clovis, Credit Suisse analysis*

# Companion Diagnostics

## (Credit Suisse Life Sciences & Tools Team)

## Companion diagnostic market has taken time to develop, but tipping point may have arrived

One of the ultimate examples of diagnostics contributing to personalized medical care is through the use of companion diagnostics. Companion diagnostics are tests that are developed in conjunction with a specific drug therapy, with the results of the test determining whether or not the patient would be a good candidate for that particular drug.

The field of companion diagnostics has been met with some skepticism by investors, given the lack of clinical impact that the approach has made over the past 15 years. In 1998, the Genentech cancer drug Herceptin was approved to treat women with metastatic breast cancer who have tumors that overexpress a protein called HER2. In conjunction with the drug approval, the FDA also approved a diagnostic test from Dako called the HercepTest that screened for this overexpression of HER2. The use of the diagnostic test to help select appropriate patients for Herceptin therapy has contributed to Herceptin becoming a blockbuster drug, with annual sales in excess of $5 billion. August 2011 may turn out to be an important tipping point in companion diagnostics, however, as the FDA approved two new cancer drugs (Zelboraf and Xalkori) in conjunction with companion diagnostic tests, with both drugs expected to become blockbusters. (See Exhibit 44.)

**Exhibit 44: August 2011 FDA Approvals of Zelboraf and Xalkori Have Increased Enthusiasm for Companion Diagnostic**

| Drug | Pharma Company | Companion Diagnostic Test | Diagnostic Company | Comments |
|---|---|---|---|---|
| Zelboraf (vemurafenib) | Roche | Cobas 4800 BRAF V600 Mutation Test | Roche | Roughly half of all metastatic melanoma tumors have a specific gene mutation called BRAF V600E in their tumor cells. This mutation leads to the tumor having an altered form of a protein call B-raf, which is involved in proper cell growth and cell death. An abnormal form of the protein can trigger the changes in the cell that result in melanoma.<br><br>The Cobas 4800 BRAF V600 Mutation Test determines whether or not a particular patient's melanoma has the BRAF V600 mutation or not. Zelboraf is a kinase inhibitor that inhibits various types of BRAF kinases, including BRAF V600E. In controlled clinical trials, Zelboraf has been shown to extend the lives of patients with melanoma that has the BRAF V600E mutation. Tumors that do possess the mutation have been found respond very well to Zelboraf therapy and the drug is only approved for use in these particular patients.<br><br>There is no data supporting the use of Zelboraf in patients who do not have the BRAF V600E mutation. Using the drug in these patients may lead to no clinical benefit while still exposing patients to the potential side effects and costs of therapy. |
| Xalkori (crizotinib) | Pfizer | Vysis ALK Break Apart FISH Probe Kit | Abbott | About 3-5% of patients with non-small cell lung cancer (NSCLC) have chromosomal rearrangements of a gene called ALK. When present, this mutation in the ALK gene can begin the process that leads to the changes that result in NSCLC.<br><br>The Vysis ALK Break Apart FISH Probe Kit can be used to detect the presence of a chromosomal arrangement in the ALK gene. Xalkori is kinase inhibitor that inhibits receptor tyrosine kinases, including ALK. In controlled clinical trials, Xalkori has been shown to lead to positive responses in patients who have the ALK mutation and the drug is only approved for use in these particular patients.<br><br>There is no data supporting the use of Xalkori in patients who do not have the ALK mutation. Using the drug in these patients may lead to no clinical benefit while still exposing patients to the potential side effects and costs of therapy. |

*Source: FDA website, Company data, Credit Suisse estimates.*

The approvals of Zelboraf and Xalkori highlight several important issues related to the development of drugs in conjunction with a companion diagnostic test:

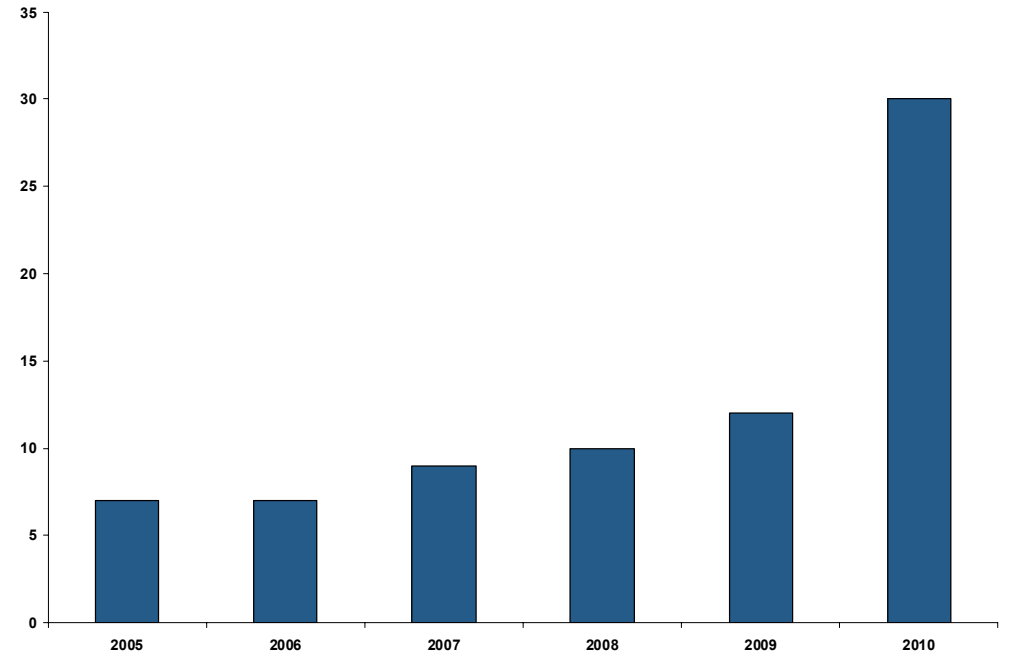
- **Greater Efficacy:** Proactively identifying the patients who were most likely to respond to Zelboraf and Xalkori allowed the clinical studies to have much more positive response rates than what has been seen previously in melanoma and non-small cell lung cancer (NSCLC), respectively.
- **More Favorable Benefit/Risk Profile:** Both drugs have the potential for causing serious side effects. However, because the drugs were tested only in patients that

were most likely to have a positive response, the overall benefit/risk ratio for the drugs is acceptable, as the overall chances of having positive efficacy results outweigh the likelihood of developing serious safety issues.

- **Higher Probability of Regulatory Success:** Generating better responses than what has been seen previously made it far more likely that regulators would approve the drugs for commercial use. This would not have been the case if the drugs were tested in all patients with melanoma or NSCLC and the results were diluted by patients without the proper mutation who do not end up having positive responses.
- **Faster Drug Development, Especially in Areas of Unmet Medical Need:** The compelling overall results for both drugs in conditions where there has been a significant unmet medical need led to the FDA approving both drugs ahead of schedule. It is fair to assume that both drugs probably made it to the market a few years earlier than they would have if they had been developed using the traditional model of drug development in which they would have been tested on all patients with melanoma or NSCLC and had less convincing clinical results.
- **Opportunity for Premium Drug Pricing:** The value proposition that Zelboraf and Xalkori offer to patients whose tumors have the appropriate genetic composition have provided Roche and Pfizer, respectively, with the ability to charge a premium price for their products. Zelboraf costs $9,400 per month, while Xalkori costs $9,600 per month. Despite being used in targeted groups of patients within the larger melanoma and NSCLC populations, this level of pricing has led the Credit Suisse U.S. and EU pharma teams to estimate that both products could generate annual sales in excess of $1 billion.

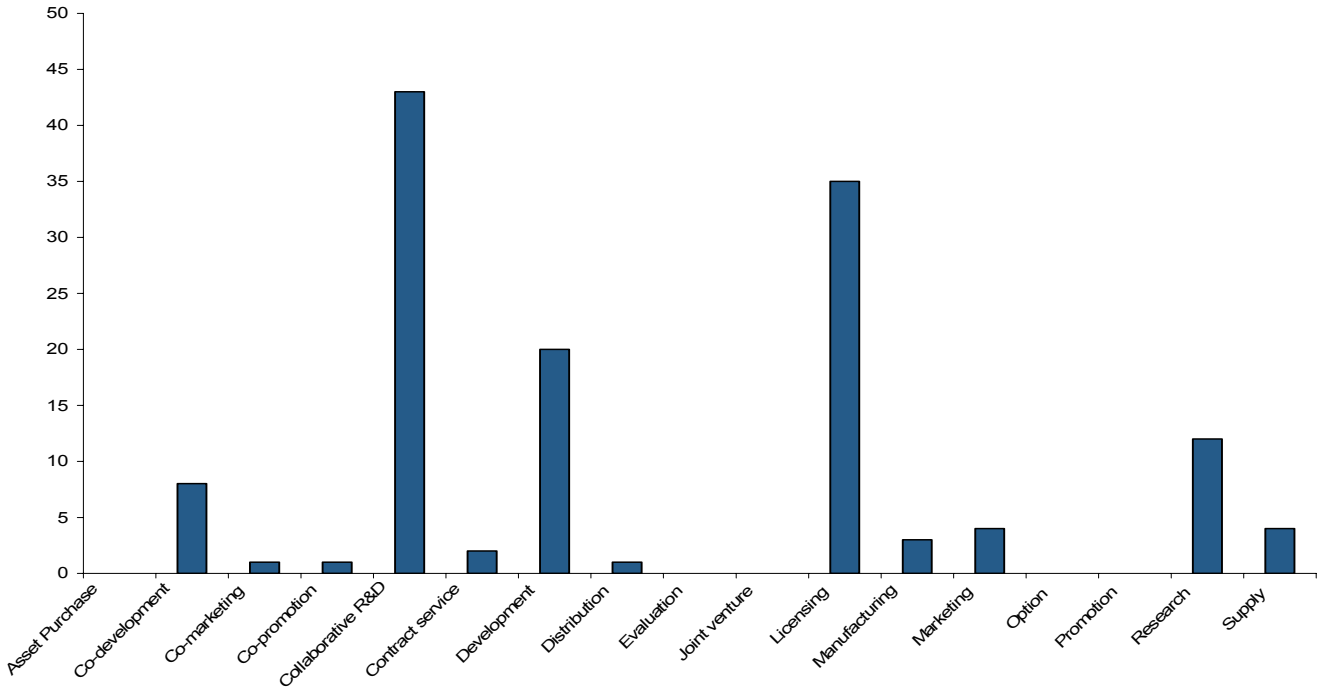
The growing excitement for companion diagnostics is evident from the surge in partnership agreements over the past several years, especially in the areas of oncology and, less so, infectious diseases and central nervous system disorders. (See Exhibit 45 - Exhibit 48.)

**Exhibit 45: Companion Diagnostic Partnering Agreements Since 2005**



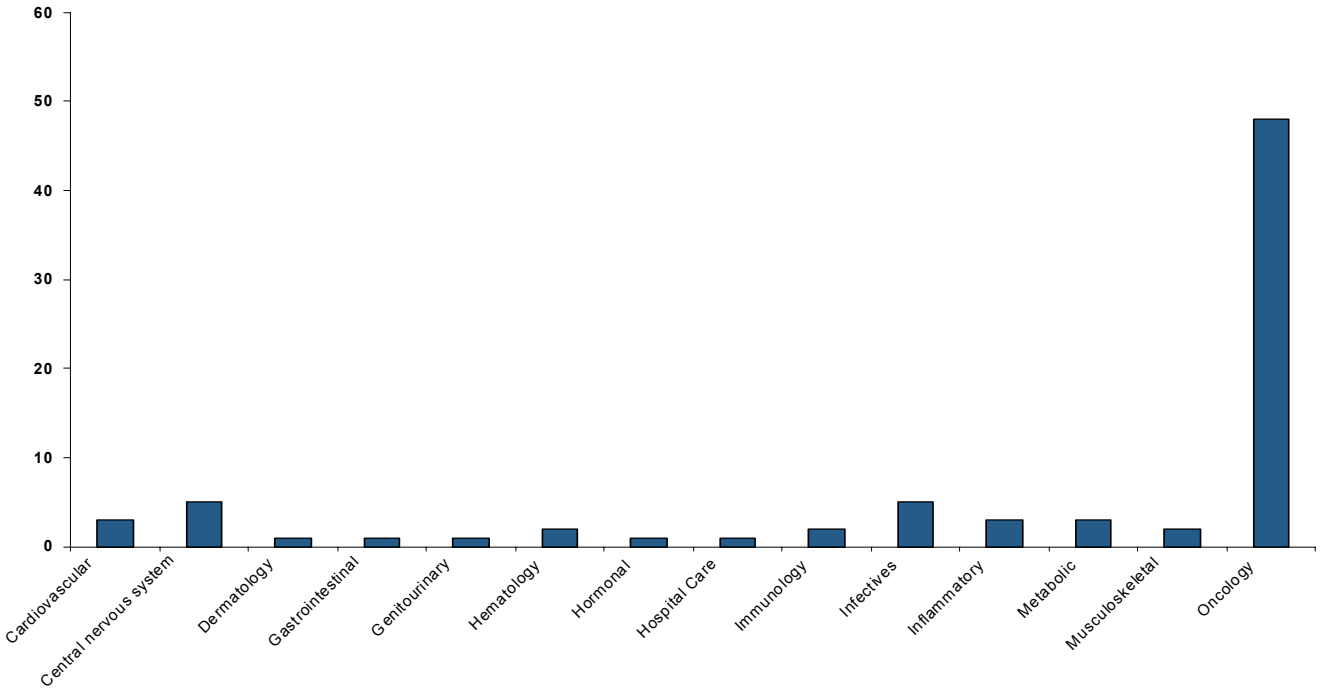

*Source: Current Partnering Companion Diagnostics Partnering Terms and Agreements January 2011, Credit Suisse estimates.*

**Exhibit 46: Companion Diagnostic Partnering by Deal Type Since 2005**



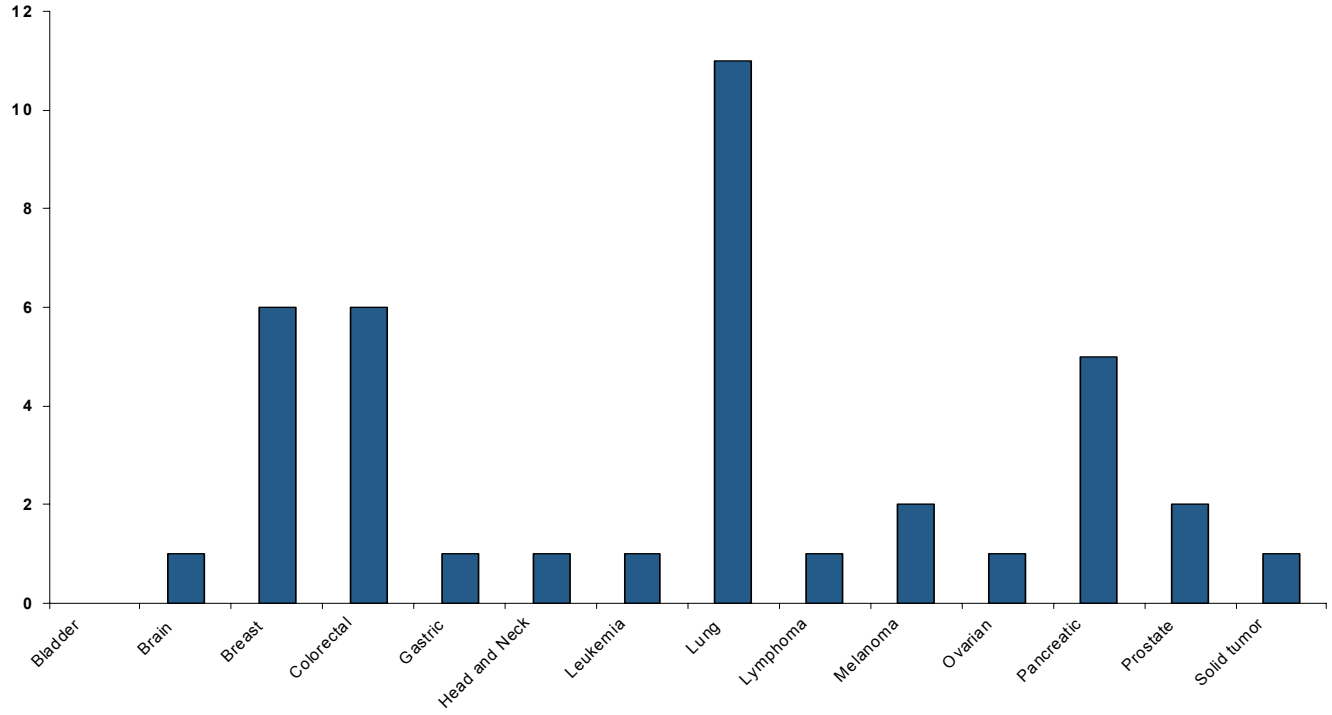

*Source: Current Partnering Companion Diagnostics Partnering Terms and Agreements January 2011, Credit Suisse estimates.*

**Exhibit 47: Companion Diagnostic Partnering by Disease Type Since 2005**




*Source: Current Partnering Companion Diagnostics Partnering Terms and Agreements January 2011, Credit Suisse estimates.*

**Exhibit 48: Companion Diagnostic Partnering by Oncology Target Since 2005**




*Source: Current Partnering Companion Diagnostics Partnering Terms and Agreements January 2011, Credit Suisse estimates.*

**Companies Mentioned** *(Price as of 04 Jan 12)*
AB Science SA (ABS.PA)
Abbott Laboratories (ABT, $56.50, NEUTRAL, TP $56.00)
Agennix AG (AGXG.DE)
Amgen Inc. (AMGN, $63.76, RESTRICTED)
ArQule Inc. (ARQL, $5.53)
Astellas Pharma (4503, ¥3,140, OUTPERFORM, TP ¥3,700, MARKET WEIGHT)
AstraZeneca (AZN.L, 3035 p, UNDERPERFORM, TP 2,600.00 p)
AVEO Pharmaceuticals, Inc. (AVEO)
Bayer (BAYGn.DE, Eu51.50, OUTPERFORM, TP Eu56.00)
Bristol-Myers Squibb (BMY, $34.34, NEUTRAL, TP $34.00)
CanBas Co Ltd. (4575.T)
Celgene (CELG, $67.92, NEUTRAL, TP $62.00)
Clavis Pharma ASA (CLAVIS.OL)
Clovis Oncology, Inc. (CLVS, $14.03, OUTPERFORM, TP $21.00)
Cyclacel Pharmaceuticals, Inc. (CYCC)
CytRx Corp. (CYTR)
Daiichi Sankyo (4568, ¥1,524, UNDERPERFORM, TP ¥1,200, MARKET WEIGHT)
Eisai (4523, ¥3,185, UNDERPERFORM, TP ¥1,700, MARKET WEIGHT)
Eli Lilly (LLY, $40.71, NEUTRAL, TP $37.00)
Endocyte Inc. (ECYT)
Exelixis, Inc. (EXEL, $4.49)
Geron Corp (GERN, $1.55)
GlaxoSmithKline (GSK.L, 1483 p, NEUTRAL, TP 1,340.00 p)
Human Genome Sciences (HGSI, $7.02, OUTPERFORM [V], TP $25.00)
Immunomedics, Inc. (IMMU, $3.33)
Infinity Pharmaceuticals Inc.. (INFI, $8.31)
Isis Pharmaceuticals, Inc. (ISIS, $7.19)
Medivation (MDVN, $45.84)
Merck & Co. (MRK, $38.34, OUTPERFORM, TP $44.00)
Merck KGaA (MRCG.DE, Eu78.40, NEUTRAL, TP Eu70.00)
Micromet, Inc. (MITI)
Neopharm, Inc. (NEOL)
NewLink Genetics Corp. (NLNK)
Novartis (NOVN.VX, SFr54.50, OUTPERFORM, TP SFr61.00)
Oncolytics Biotech Inc. (ONC.CN)
Oncothyreon Inc. (ONTY, $7.32)
Onyx Pharmaceuticals, Inc. (ONXX, $42.83)
Otsuka Holdings (4578, ¥2,179, NEUTRAL, TP ¥2,300, MARKET WEIGHT)
Peregrine Pharmaceuticals (PPHM)
Pfizer (PFE, $21.77, OUTPERFORM, TP $23.00)
Pharmacyclics, Inc. (PCYC)
Rexahn Pharmaceuticals Inc. (RNN)
Roche (ROG.VX, SFr162.70, OUTPERFORM, TP SFr180.00)
Sanofi (SASY.PA, Eu56.21, NEUTRAL, TP Eu54.00)
Spectrum Pharmaceuticals, Inc. (SPPI)
Teva Pharmaceutical Industries (TEVA, $43.55, OUTPERFORM, TP $53.00)
Threshold Pharmaceuticals Inc. (THLD)
Transgene SA (TRNG.PA)
YM Biosciences Inc. (YMI)
ZIOPHARM Oncology, Inc. (ZIOP)

# Disclosure Appendix

**Important Global Disclosures**

I, Ravi Mehrotra PhD, certify that (1) the views expressed in this report accurately reflect my personal views about all of the subject companies and securities and (2) no part of my compensation was, is or will be directly or indirectly related to the specific recommendations or views expressed in this report.

*See the Companies Mentioned section for full company names.*

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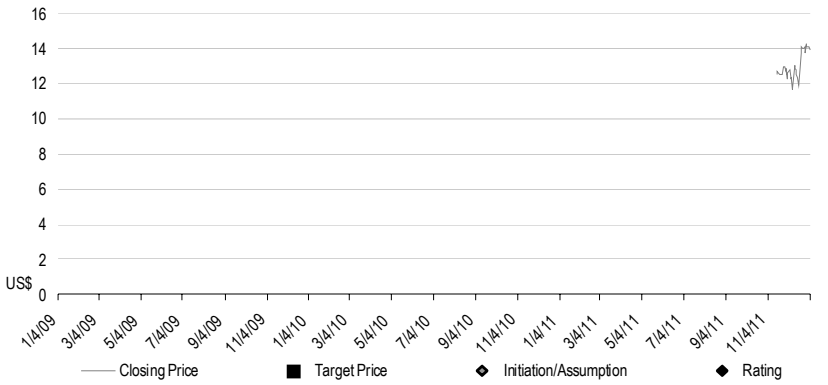
**3-Year Price, Target Price and Rating Change History Chart for CLVS**

| CLVS Date | Closing Price (US$) | Target Price (US$) | Rating | Initiation/ Assumption |
|---|---|---|---|---|




O=Outperform; N=Neutral; U=Underperform; R=Restricted; NR=Not Rated; NC=Not Covered

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**Outperform (O):** The stock's total return is expected to outperform the relevant benchmark* by at least 10-15% (or more, depending on perceived risk) over the next 12 months.

**Neutral (N):** The stock's total return is expected to be in line with the relevant benchmark* (range of ±10-15%) over the next 12 months.

**Underperform (U):** The stock's total return is expected to underperform the relevant benchmark* by 10-15% or more over the next 12 months.

**Relevant benchmark by region: As of 29th May 2009, Australia, New Zealand, U.S. and Canadian ratings are based on (1) a stock's absolute total return potential to its current share price and (2) the relative attractiveness of a stock's total return potential within an analyst's coverage universe**, with Outperforms representing the most attractive, Neutrals the less attractive, and Underperforms the least attractive investment opportunities. Some U.S. and Canadian ratings may fall outside the absolute total return ranges defined above, depending on market conditions and industry factors. For Latin American, Japanese, and non-Japan Asia stocks, ratings are based on a stock's total return relative to the average total return of the relevant country or regional benchmark; for European stocks, ratings are based on a stock's total return relative to the analyst's coverage universe**. For Australian and New Zealand stocks, 12-month rolling yield is incorporated in the absolute total return calculation and a 15% and a 7.5% threshold replace the 10-15% level in the Outperform and Underperform stock rating definitions, respectively. The 15% and 7.5% thresholds replace the +10-15% and -10-15% levels in the Neutral stock rating definition, respectively.*

***An analyst's coverage universe consists of all companies covered by the analyst within the relevant sector.*

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**Market Weight:** Industry expected to perform in-line with the relevant broad market benchmark over the next 12 months.

**Underweight:** Industry expected to underperform the relevant broad market benchmark over the next 12 months.

**An analyst's coverage universe consists of all companies covered by the analyst within the relevant sector.*

***The broad market benchmark is based on the expected return of the local market index (e.g., the S&P 500 in the U.S.) over the next 12 months.*

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|---|---|---|
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| **Underperform/Sell*** | 10% | (51% banking clients) |
| **Restricted** | 2% | |

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**Price Target:** (12 months) for (CLVS)
**Method:** Our target price of $21 for CLVS is derived using a discounted cash flow (DCF) methodology, assuming a discount rate of 10%, annual cash flows on CO-101 until 2021, 50% probability of success for CO-101, and no terminal value.
**Risks:** Key risks to our $21 target price for CLVS are (1) CO-101 is not approved in the U.S. and/or EU, (2) Launch of CO-101 is significantly delayed, (3) Readout from the pivotal LEAP trial is worse than expected, (4) Clovis fails to raise funds in 2013 to continue operations, (4) Dilution from anticipated financing in 2013 is worse than expected, and (5) CO-101 could underperform our expectations commercially.

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