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Biotechnology (Citi)
Global

PARP Inhibitors For Cancer Hit Prime Time

Tesaro is Best Pure Play; BioMarin Offers More Modest Exposure But Spreads Risk Across Its Deep and Promising Pipeline

- **Conclusion** — We have conducted a deep dive on the market potential of PARP inhibitors for ovarian and breast cancers. We believe that this is an exciting but overlooked new class of drugs that provides a good investment potential. PARP inhibitors have shown very exciting results in clinical trials that target patients with mutation in the "breast cancer genes" (BRCA-1/2). BRCA-1 recently garnered public attention following actor Angelina Jolie's announcement that she had a double mastectomy since she has the BRCA-1 gene mutation that confers a high risk of developing breast cancer. We believe that Tesaro (TSRO) and BioMarin (BMRN) are best positioned to play the PARP inhibitor theme. Of the two, Tesaro is a pure play while BioMarin offers a more modest exposure but spreads the risk across its deep pipeline.
- **PARP Inhibitors' Clinical Profile**— PARP inhibitors are highly active as single agents in specific well defined subsets of cancer patients with BRCA 1/2 gene mutations. These drugs should offer superior potency and much better tolerability compared to traditional chemotherapy. PARP inhibitors should garner premium pricing ($12.5k-$15k/month) and offer attractive margins. Their clinical profile should support broad and rapid uptake following approval.
- **Key Differentiation Points Are Not Just Clinical** — BMN-673 is the most potent PARP inhibitor based on cell culture assays, but it is slightly earlier in development compared to AstraZeneca and Tesaro. At this stage, all PARP inhibitors look very similar in terms of clinical efficacy and we do not anticipate that data at the upcoming ASCO meeting will necessarily differentiate them based on potency. Instead, time to market, development strategy, and profitability impact on each stock lead us to favor Tesaro and BioMarin.
- **Who's On First?** — AstraZeneca's olaparib is the most advanced PARP. We expect approval in Europe in H2:14 based on ph 2 data in ovarian cancer. The race to market for both ovarian and breast cancers is tight with AstraZeneca, Tesaro and BioMarin leading the pack with approval expected in 2017 in US/EU. Clovis Oncology is employing a different strategy that is based on developing a new assay that will likely delay approval until 2018 but will provide some differentiation if that new assay is needed. At this point, for ovarian cancer, it looks like all drugs offer similar potency so time to market is key and it is not clear that a new diagnostic assay will provide an edge. BioMarin is currently only focusing on breast cancer while Clovis is focusing on ovarian cancer. Only AZN and Tesaro are focusing on both segments.
- **PARP Inhibitor Has Shown Solid Potency in Ovarian and Breast Cancers –** The data shows that PARP inhibitors should work as maintenance therapy in ovarian cancer and should be able to show superiority to chemo in breast cancer. We model ~$3B in peak global sales among the 4 drugs.
- **Playing the PARP Space** — Tesaro (TSRO) and BioMarin (BMRN) are our best ideas for this new market. Of the two, Tesaro is more of a pure play while BioMarin has exposure but is more diversified. We raised Tesaro's TP to $43 (+$12) as we added $1.1B in probability-adjusted sales in ovarian and breast cancer for niraparib to our model. We raised BioMarin's TP to $79 (+$7) as we updated our SOTP analysis and add $440M in peak probability-adjusted sales for BMN-673 in breast cancer.
- **Conf Call: PARP Expert Tomorrow @ 10AM ET** — #: 719-457-6823, pwd: 5113296.

■ Industry Overview

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PARP Inhibitors For Cancer – How to Invest in This Lucrative Opportunity

- **PARP inhibitors are now hitting prime time after several unsuccessful initial starts.**
- **This class of drugs targets specific patients populations that have identifiable genetic mutations (ie personalized medicine approach) or specific subset of cancer (for ex high grade serous ovarian cancer).**
- **PARP inhibitors specifically target patients with mutation in the breast cancer gene called BRCA 1/2. Angelina Jolie recently brought attention to this gene by announcing that she had a double mastectomy (removal of both breasts) since she had the BRCA 1 gene mutation identified in her.**
- **They are highly active as single agents, are backed by solid data, and are very well tolerated. This sets them apart from traditional chemotherapy that has weaker activity and much more side effects.**
- **As these drugs target a specific subset of patients, they can garner premium pricing ($12.5k-$15k/month) and offer solid margins.**
- **We believe that Tesaro (TSRO) is the best "pure" play on the PARP inhibitor theme as the company is only focused on cancer and can use its pre-existing global infrastructure to market niraparib.**
- **We are raised our target price on Tesaro to $43 (+$12) supported by our peak sales estimate of $1.1B for niraparib (60-65% probability of success).**
- **BioMarin's BMN-673 is very promising but will only target breast cancer initially. Thus, this drug will likely generate only probability-adjusted $440M in global sales. Our new target price is $79 (+$7) of which +$5 is due to including BMN-673 in our model. BioMarin offers more modest exposure to the PARP theme and we like the stock for its deep and promising pipeline.**

PARP Inhibitors Hit Prime Time

This is the next exciting family of anti-cancer drugs to watch and support our bullish view on Tesaro (TSRO) and BioMarin (BMRN). BioMarin is on Citi's Top Picks Live (TPL) list. Citi's Biotech Team does not cover Clovis Oncology (CLVS).

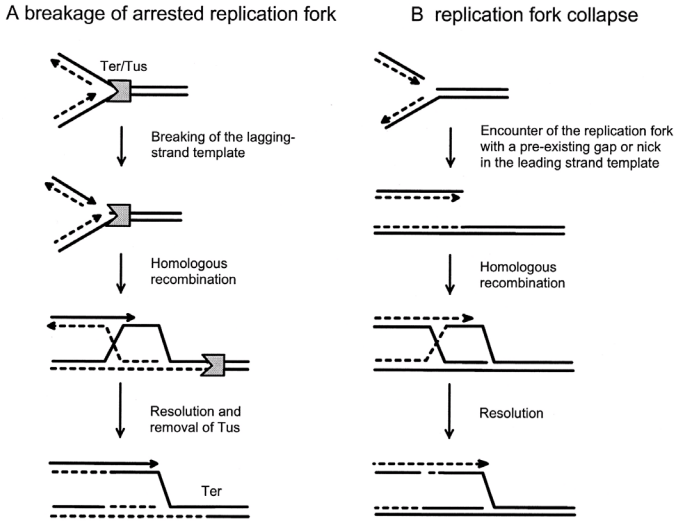
Poly (ADP-ribose) polymerase (PARP) is a nuclear enzyme that coordinates base excision repair (BER) to fix single-stranded DNA breaks. The enzyme directly binds to sites of DNA damage to recruit other DNA repair enzymes.

Given that DNA damage occurs frequently during cell division, the PARP enzyme has a vital function in DNA repair to ensure the survival of the cell. As a result, this enzyme could be a very promising anti-cancer target.

During the DNA repair process, a process that is commonly employed is called homologous recombination. Interestingly, certain cells develop mutations in their homologous recombination enzymes and these defects (homologous recombination defects, aka HRD) are potential targets for PARP inhibitors.

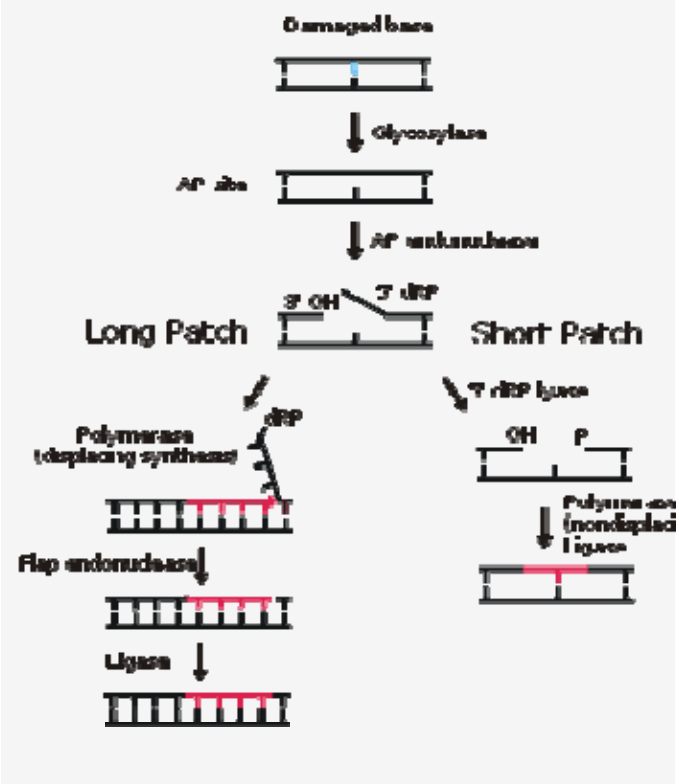
The BRCA 1 & 2 mutations are thought to be good biomarkers for underlying HRD and there is ample clinical data to provide proof that targeting the PARP enzyme can be therapeutically beneficial in ovarian and breast cancers that harbor these mutations (aka BRCAmut or BRCA +).

Figure 1. Homologous Recombination Repair



Source: Michel B et al. PNAS 2001;98:8181-8188

Figure 2. Base Pair Excision Repair (BER)



Source: Wikipedia

Figure 3. Synthetic Lethality

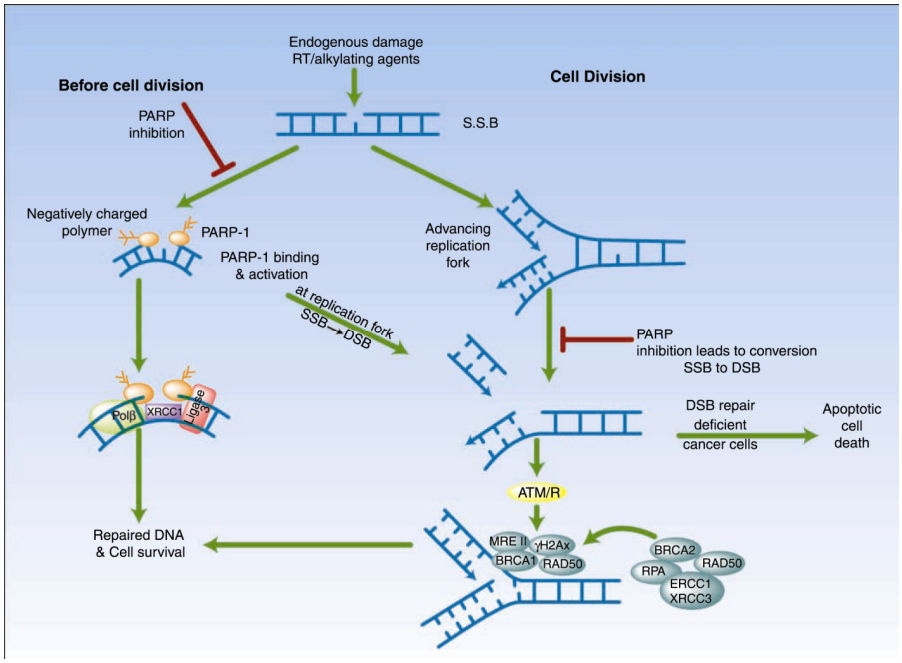
Homologous Recombination Defect (HRD)	PARP Inhibition	Outcome
-	-	Cell survives
-	+	Cell survives
+	-	Cell survives
+	**+**	**Cell death**

Source: Citi Research

PARP Inhibitors – Taking Advantage of Synthetic Lethality

PARP inhibitors take advantage of a mechanism called as synthetic lethality to target cancer cells. Synthetic lethality occurs if two genetic mutations are nonlethal when they occur individually, but lead to cell death when they occur in combination. For example if PARP activity is impaired, other DNA repair pathways take over to repair the resulting DNA damage. However, if PARP inhibitors are used in tumors that already have defects in other DNA repair pathways, then the combination becomes synthetically lethal.

Figure 4. Mechanism of PARP Inhibition in Cell Death



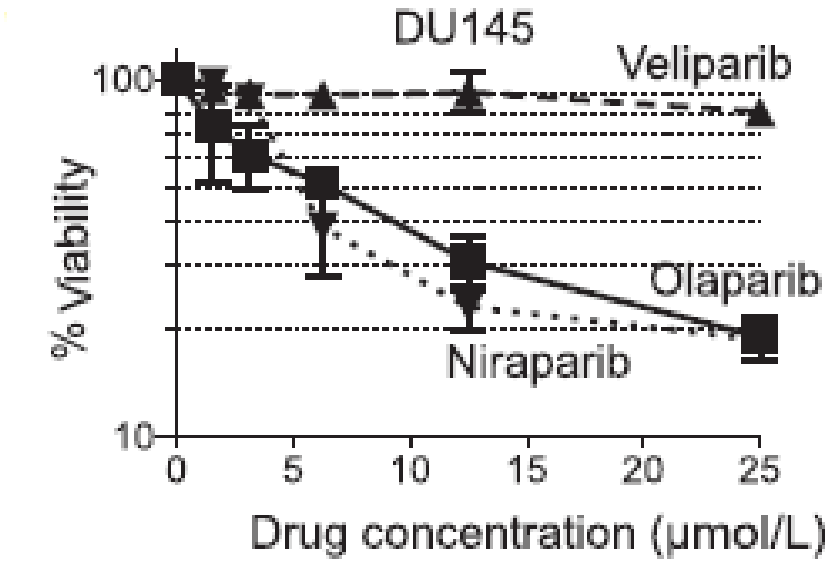
Source: ASCO 2011

PARP's New Mode of Action- Trapping PARP to Damaged DNA

Recently, new research has shown that PARP inhibitors work by not only inhibiting the PARP enzyme and propagating damage to DNA, but also trap the PARP enzyme unto the damaged DNA. The data shows that trapped PARP–DNA complexes are more cytotoxic than unrepaired single strand breaks caused by PARP inactivation.

What is intriguing is that the potency of a drug in trapping the PARP enzyme on DNA is not correlated with the catalytic inhibitory properties for the drug. This suggests that the activity is secondary and is likely based on the side chains of the drug.

Figure 5. Niraparib More Potent in Killing Cells



Source: Murai et al. Cancer Research 2012.

Based on a cell assay experiment, Tesaro's niraparib has the highest potency to trap PARP on damaged DNA followed by AstraZeneca's olaparib, while AbbVie's veliparib had the least potency.

Angelina Jolie has the BRCA-1 ("breast cancer gene") mutation that led to her well publicized and courageous decision to have a double mastectomy as she had a high risk of developing breast cancer.

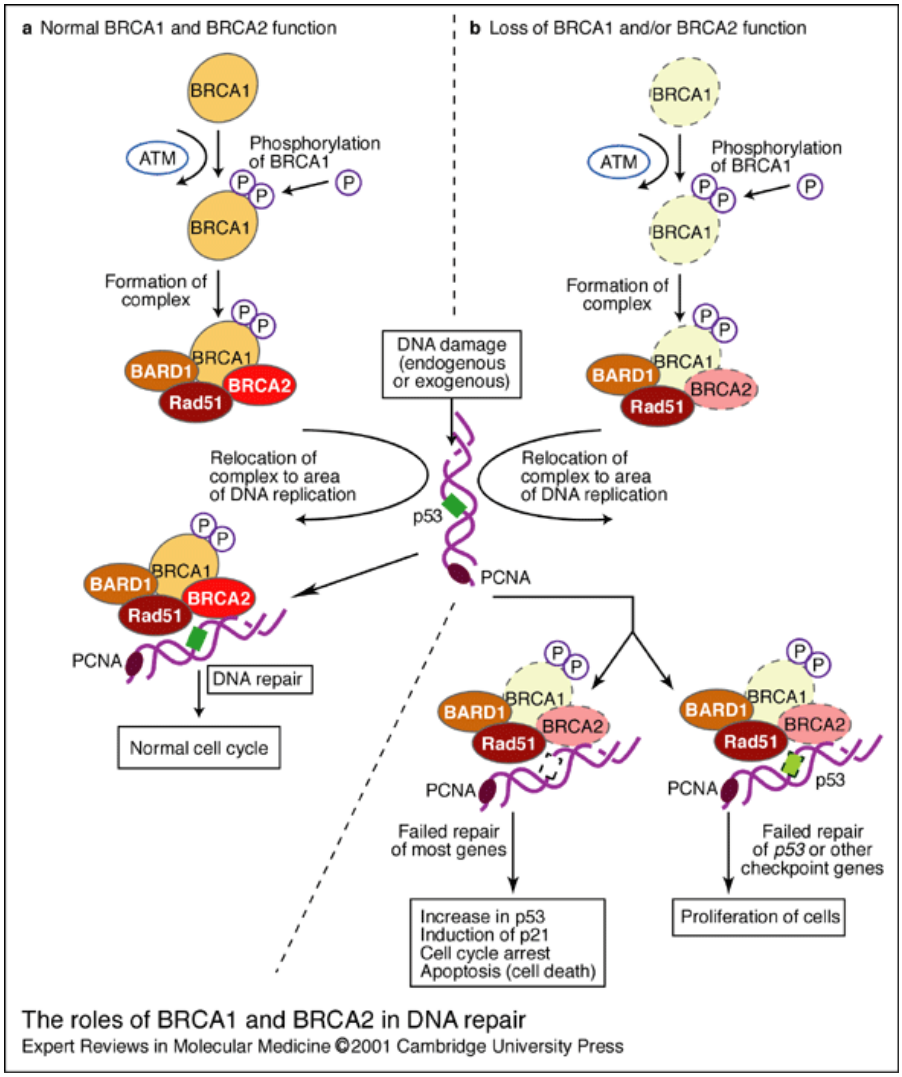
BRCA1 and BRCA2 Deficient Cells Are Sensitive to PARP Mutations

Breast cancer type 1 and 2 susceptibility proteins (BRCA1 and BRCA2) are enzymes that are important for the normal repair of double-stranded DNA in cells. BRCA defective cells lose their capacity for homologous recombination, so they are more dependent on BER. In the presence of a PARP inhibitor, BRCA deficient (aka mutant) cells are unable to repair single stranded DNA breaks, leading to double stranded breaks and eventually cell death.

In cell cultures, the inhibition of PARP in BRAC1 and 2 cells results in cell death (cytotoxicity). This data suggests that BRAC + tumors should be sensitive to PARP inhibitors even when those are used as monotherapy.

Recent clinical results in both BRCA + ovarian and breast cancers have been promising and this validates this approach. We anticipate that phase 3 studies will commence shortly with several PARP inhibitors in ovarian and breast cancers.

Figure 6. Role of PARP in BRCA 1/2 Mutations



Source: Expert Reviews in Molecular Medicine, 2001

Currently, Myriad Genetics is working on a new blood-based assay that will detect a broader set of HRD mutations.

Myriad already markets the currently available BRCA 1/2 blood test.

Separately, Foundation Medicine and Clovis Oncology are collaborating on developing a tissue-based germ-line vs somatic assay to detect BRCA 1/2 mutations as well as validate a broader set of HRD mutations.

PARPs Might Be Active in a Wider Array of Mutations

Since BRCA 1/2 mutations likely work via the homologous recombination defect (HRD) pathway, it is expected that a wider array of HRD mutations should also be sensitive to PARP inhibition.

Recent data suggests that the post replication repair, Fanconi anemia pathway, polymerase b, and FEN1 are critical for repairing trapped PARP–DNA complexes.

PARP Inhibitors Have a Mixed History – Sanofi's Iniparib Failed

PARP inhibitors have historically garnered a lot of attention, but the initial excitement quickly faded following disappointing early results, difficulty in finding the correct dosing scheme, and formulation issues.

The first PARP inhibitor to disappoint was Sanofi's iniparib that failed in ph 3 in combination with chemo for triple negative breast cancer. This data was surprising. But later it was found that iniparib was not a potent PARP inhibitor and it was also noted that targeting an unselected triple negative breast cancer is not a sound strategy.

A germ-line mutation is a mutation that a woman was born with.

A somatic mutation is a newly acquired (ie develops after birth) mutation.

Initial Data With AstraZeneca's Olaparib is Highly Promising

At ASCO 2009, AstraZeneca showed interim ph 2 data of their PARP inhibitor olaparib showing 40% response rates in BRCA+ women with triple negative breast cancer and 33% in BRCA+ ovarian cancer. Based on this data a second ph 2 trial was conducted without identification of a patients' BRCA status. Unfortunately, this study did not show benefits in overall survival. It has been noted that perhaps the second ph 2 trial of Olaparib would have succeeded if only BRCA+ patients were included.

Olaparib Re-Emerges Driven By Ledermann's Ph 2 Study in Ovarian Cancer Showing Clear Activity in High Grade Serous Ovarian Cancer

In a separate ph 2 study conducted by Ledermann et al, olaparib showed solid activity in high-grade serous ovarian cancer women who are platinum-sensitive. The data showed a clear PFS benefit, by did not show an overall survival benefit.

This data was initially viewed as disappointing since it did not yield an overall survival benefit. But as more evidence emerged showing that PARP inhibitors are clearly very active in BRCA+ and high grade serous ovarian cancer patients, the academic community then reconsidered its initial view and came to appreciate the pronounced effect on PFS was better appreciated.

EMA Encourages AstraZeneca to File For Approval Based on Phase 2

AstraZeneca will file olaparib in Europe based on ph 2 data for ovarian cancer. In the U.S., a ph 3 study will likely be required for approval.

Based on this data, the European Medicines Agency (EMA) encouraged AstraZeneca to file for approval in Europe. AstraZeneca will likely file in 2013 and will separately shortly commence a ph 3 study to support filing in the U.S.

The Race is On Between AstraZeneca, Tesaro, BioMarin and Clovis

Since olaparib's ph 2 in ovarian cancer, solid data from Merck's niraparib was announced. This led Tesaro to in-license niraparib (potent PARP inhibitor) from Merck. Clovis Oncology also in-licensed rucaparib from Pfizer and has reformulated the drug from IV to an oral form. Finally, BioMarin's BMN-673 is currently completing its ph 1/2 study and we expect positive data at ASCO 2013 in early June.

ASCO Will Be the Coming Out Party For PARP Inhibitors

ASCO is looking to be very interesting for the PARP class of drugs as 4 drugs are ready to move into ph 3. AstraZeneca and Tesaro will each start ph 3 in ovarian cancer shortly testing the activity of olaparib and niraparib in 2 different patient populations (HGSOC vs BRCA+).

All four PARP drugs have show very good single agent activity and solid tolerability in ovarian, breast and gastric cancers. We expect to see positive phase 2 data from all these drugs as ASCO on June 2-4th (please see our recent note).

AstraZeneca will likely also start ph 3 studies in breast and gastric cancers while Tesaro will soon start a ph 3 in BRCA+ breast cancer.

BioMarin is slightly behind and will likely start ph 3 in Q4:13 in breast cancer. Clovis' rucaparib is adopting a slightly different strategy and will commence a ph 2 biomarker validation study in Q3:13 in ovarian cancer and ph 3 in HGSOC ovarian cancer in Q4:13.

Figure 7. PARP Inhibitors

Drug (Company)	Dose	Dosing Frequency
Olaparib (AZN)	300mg	Twice daily
Niraparib (TSRO)	300mg	Once daily
BMN-673 (BMRN)	1mg	Once daily
Rucaparib (CLVS)	480mg?	Twice daily

Source: Citi Research

BioMarin's BMN-763 is an Optimized PARP Inhibitor

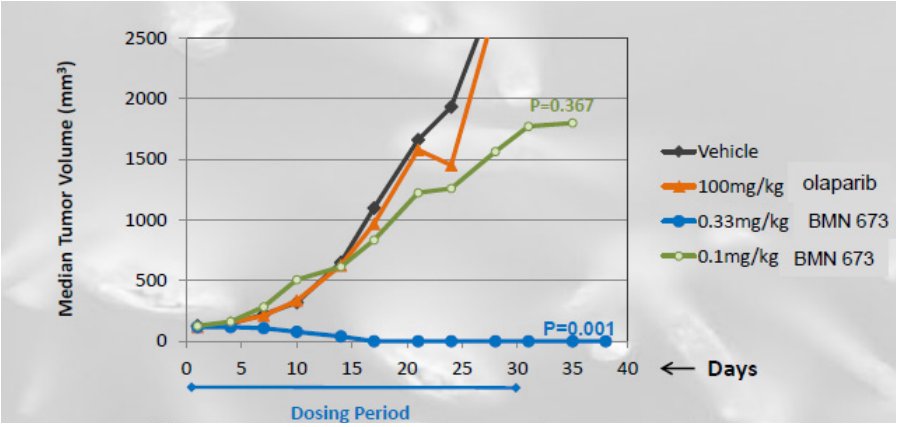
BMN-673 is the most potent PARP inhibitor with the lowest nM single agent inhibition of tumor cells with DNA repair defects. This means that this drug requires the lowest dose of all PARP inhibitors to cause the maximal tumor killing. BMN-673 has a high oral bioavailability and solid anti-cancer activity.

While the drug is very potent and likely has a wide therapeutic window, it does not necessarily mean that it will be the most effective in clinical studies.

Thus far, BMN-673 also showed very impressive overall response rates in ovarian and breast cancers in early stage studies. But we note that the other drugs have shown fairly impressive results as well that seem to be on par albeit all the data is very early and very hard to evaluate. At this point, it is too early to try to make differentiation among the drugs based on their initial response rate data.

Since all these drugs have the key limiting toxicity of myelosuppressive (reduction in white blood cell counts), it remains to be seen whether BMN-673's higher potency in cell culture assays will ultimately lead to differential potency in clinical studies.

Figure 8. BMN-673 Shows Faster Reduction of Tumor Volume Than Olaparib



Source: BioMarin Data

Based on cell culture data, BMN-673 looks the most potent while olaparib, niraparib and rucaparib look comparable. AbbVie's veliparib is the least potent and is being tested with chemo since it does not have ample single agent activity.

Based on the cell culture experiments, we view niraparib, olaparib, and rucaparib to be fairly comparable in terms of their single agent activity while BMN-673 is most potent (see Figure 9).

Figure 9. Relative Potency of PARP Inhibitors

Drug	PARP-1 Enzyme Inhibition IC50 (nM)	Cellular PAR Synthesis EC50 (nM)	Temozolomide Potentiation GI50 (nM)	Capan-1 (brca2 -/-) Cytotoxicity IC50 (nM)
Veliparib	4.73	5.94	6,203	>10,000
Rucaparib	1.98	4.69	144	609
Olaparib	1.94	3.56	237	259
BMN-673	0.57	2.5	4	5
Niraparib	3.8	4		

Source: Citi Research

Combo of PARPs with Chemo Is Challenging Due to Side Effects

Combination therapy of PARP Inhibitors with chemotherapy is a very sensible approach to optimize outcomes by using complementary mechanisms of actions.

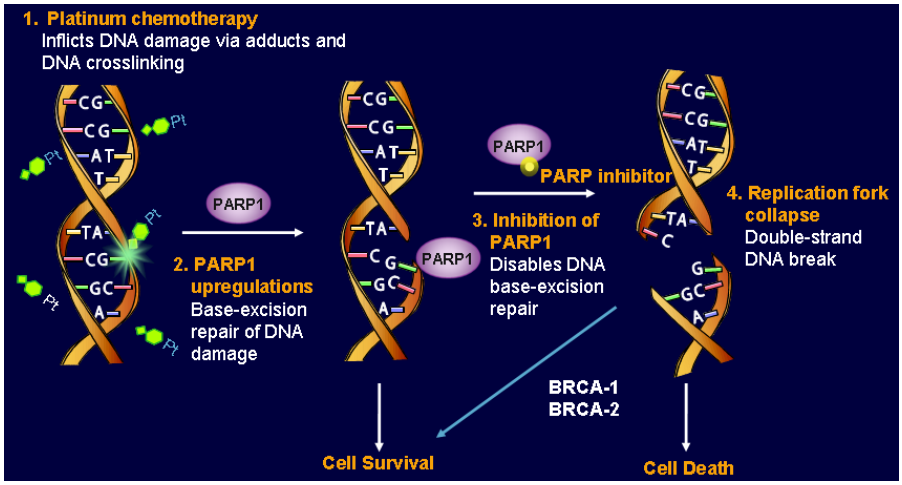
Chemotherapy typically damages the DNA of cancer cells and PARP inhibitors can disrupt the DNA repair mechanism (see Figure 10).

Olaparib has shown promising ph 2 data with chemo in gastric cancer. Ph 3 studies will likely start in 2013.

AbbVie's veliparib is not potent enough as a single agent and so the drug has been tested with chemo in breast cancer. However, in that setting, it looks like more potent PARP inhibitors can show solid activity alone without chemo and that is more attractive.

In gastric cancer, olaparib+paclitaxel will release positive ph 2 data at ASCO. AstraZeneca will start ph 3 studies with this approach in the future and that is promising.

Figure 10. PARP Inhibitors Prevent Repair of DNA Damage and Cause Cell Death



Source: ASCO 2011

Which Tumors Can PARP Inhibitors Target?

Based on results so far, the most attractive tumors are:

- Breast (monotherapy)
- Ovarian (monotherapy)
- Gastric (combo with chemo)
- Prostate cancer (BRCA sensitive subset)
- Pancreatic and colon cancers – exploratory studies underway
- Small cell lung cancer (HRD-based mechanism)
- Ewing's sarcoma – potential cancer for further study
- Glioblastoma – potential cancer for further study

Figure 11. PARP Inhibitors in Various Cancers

	Tumor	Phase		Mono or Combo	Companies	Start Ph3	Filing
Positive Data	**Ovarian**	2		Mono	AstraZeneca BioMarin Clovis Tesaro	**AstraZeneca**: Mid-'13 **BioMarin**: No plans **Clovis**: Q4:13 **Tesaro**: Mid-'13	**AstraZeneca:** File with EMA (H2:13)
	Breast	1/2		Mono	AstraZeneca BioMarin Tesaro	**AstraZeneca**: H2:13 **BioMarin**: Q4:13 **Clovis**: No plans **Tesaro**: Q4:13	
	Gastric	2		Combo	AstraZeneca	**AstraZeneca:** 2013	
Proof of Concept	**Colon**	2		Both	AbbVie AstraZeneca		
	Ewing Sarcoma	1/2		Mono	AstraZeneca BioMarin		
	Pancreatic	1/2		Both	AbbVie AstraZeneca BioMarin		
	Prostate	1/2		Mono	AbbVie AstraZeneca BioMarin Tesaro		
	Small Cell Lung Cancer	1/2		Both	AbbVie BioMarin		

Source: Citi Research

BRCA Mutation Cancers Are a Lucrative Market Opportunities in Ovarian and Breast Cancers

Based on our research, ~15% of ovarian cancers have germ-line and ~6% have somatic BRCA mutations. In addition, another 30-40% can have other HRD mutations that could be sensitive to PARP inhibitors.

Most importantly, we estimate that ~70% of ovarian cancer patients have the high grade serous subtype and of those, 70% are platinum sensitive. We peg the number of metastatic ovarian cancer patients are ~22k in the U.S. and ~21k in Europe.

In addition, 8%-10% of breast cancers have BRCA + mutations. In the US, we peg the number of metastatic breast cancer patients at ~90k and ~97k in Europe.

This suggests that the market for PARP inhibitors can be very lucrative especially given the potential for high response rates in very advanced patients. This can support premium pricing ($15k/month in the U.S. and $12.5k in Europe) and high margins.

Figure 12. # of Patients

	Ovarian	Breast
U.S.	10,702	8,952
Europe	10,253	10,253
Global	**20,955**	**19,205**

Ovarian = High grade serous, platinum sensitive

Breast = BRCAmut

Source: Citi Research

Our Model Assumptions for PARP Inhibitors

In our model, we model a 65% probability of success in ovarian cancer and slightly lower at 60% in breast cancer as there is less data in breast cancer.

We anticipate that the average duration of therapy will be 7 months in ovarian cancer and 6 months in breast cancer based on olaparib's previous results.

Figure 13. Global PARP Class Sales Ests (Probability Adjusted)

Drug	Year approved U.S	Year approved Europe	Peak Sales ($M)	Indications
Olaparib	2017	2014	$976	Ovarian/Breast
Niraparib	2017	2017	$1,081	Ovarian/Breast
BMN-673	2017	2017	$440	Breast
Rucaparib	2018	2018	$488	Ovarian
Total Global Sales			**$2,985**	

Ovarian cancer = 65% probability of success

Breast cancer = 60% probability of success

Source: Citi Research

Target Prices Raised – Tesaro More Levered on PARPs; BioMarin Provides More Downside Protection

We raised BioMarin's target price to $79 (+$7) of which $5 is due to the addition of BMN-673 to our sum of the parts (SOTP) valuation. The other +$2 change is due to updating the discounting period of the DCF.

Given that we estimate that BioMarin will have ~$440m in peak sales, assuming 10% COGS and 35% SG&A, the boost to the SOTP is $5/share.

For Tesaro, the financial leverage of niraparib appears far greater. With ~$1.1B in revenues, the potential impact on profitability is far greater. We raised our target price to $43 (+$12) as we are now including sales of niraparib in our model. Our valuation is based on 25x our new 2018 EPS estimate of $3.35 (+$1.24) discounted by 20%.

Figure 14. Raising Target Price on BioMarin (BMRN) and Tesaro (TSRO)

Company	Ticker	Target Price	Comments
BioMarin	BMRN	**$79 (+$5)**	$5 due to BMN-673 and $2 updating SOTP
Tesaro	TSRO	**$43 (+$12)**	due to adding niraparib to model

Source: Citi Research

PARP Inhibitors in Ovarian Cancer

- **PARP inhibitors have shown consistently positive results in ovarian cancer.**
- **The activity was not limited to just BRCA + ovarian tumors but also worked in the broader high grade serous ovarian cancer (HGSOC) population that is sensitive to platinum chemotherapy (~50% of all ovarian cancer patients).**
- **We see little differentiation among the 4 lead drugs from AstraZeneca, Tesaro, BioMarin and Clovis.**
- **Time to market and development strategy are key to calling the market winner. We expect that AstraZeneca will be approved in Europe in H2:14 and in the US in 2017. We anticipate that Tesaro will be approved in US/EU in 2017 and Clovis in 2018.**
- **In ovarian cancer, AstraZeneca will likely to get to market first in Europe based on ph 2 data. In the U.S., Tesaro and AstraZeneca are in a tight race. Clovis is behind and will likely lag to market due to their complex development strategy.**
- **BioMarin is not planning on focusing on ovarian cancer at the current time.**

Molecular Profile of Ovarian Cancer

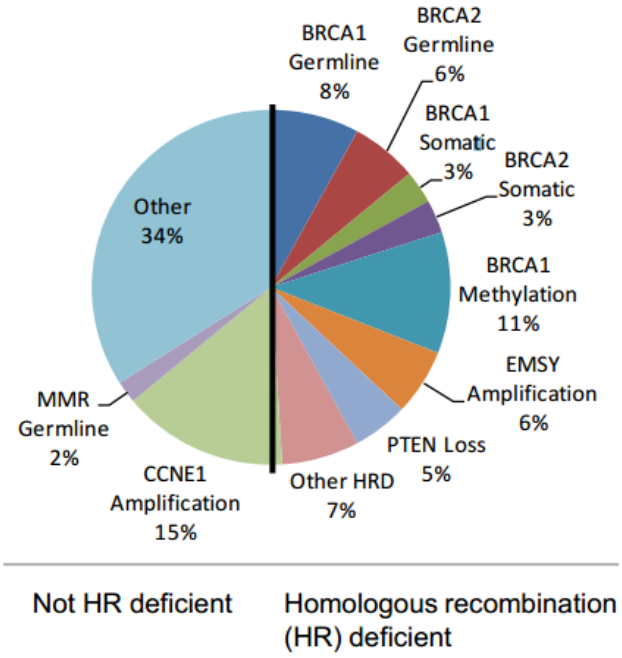
It is estimated that germ-line mutations will account for 2/3 and somatic mutations will account for 1/3 of all BRCAmut in ovarian cancer.

Based on the Cancer Genome Atlas, ~ 50% of ovarian cancers can be classified as having defects in homologous recombination (HRD) of which 20% have either germ-line or somatic BRCA1 or BRCA1 mutations (aka BRCA + or BRCAmut).

According to the data, germ-line mutations afflict 14% of all patients and somatic mutations account for an additional 6% of all mutations.

Based on many phase 2 studies, the beneficial role of PARP inhibitors has been established and this pathway has been validated, in our view.

Figure 15. Molecular Profile of High Grade Serous Ovarian Cancer



Source: Cancer Genome Project, 2011

AstraZeneca's Olaparib is Promising for Ovarian Cancer

Olaparib has completed at least 6 studies in ovarian cancer patients with or without the BRCA 1/2 mutations. The data has been encouraging and highlighted the drug's activity in terms of both response rates and progression free survival (PFS) benefit.

Initial Ledermann Ph 2 Data Was Considered a Disappointment…

The phase 2 data was initially poorly understood as olaparib failed to show an overall survival benefit likely due given that patients cross over from the placebo arm to subsequent therapies.

In addition, when the study was designed, the potential importance of the BRCAmut on clinical outcomes was not appreciated and so patients' mutational status was not investigated prospectively. This contributed to the initial confusion and disappointment with the results.

At the time of the initial Ledermann publication of the results in the NEJM, only 13% of patients in the olaparib arm and 16% of patients in the placebo arm screened have the BRCA mutation. But the BRCA mutation status of 64% of patients in the olaparib arm and 63% of patients in the placebo arm was not known.

…But Ph 2 Data Then Re-Emerged as a Success When BRCA Status Was Included as a Stratification Tool

However, as the field progressed, clinicians came to appreciate that the data was actually quiet robust in all patients who either:

1. have an underlying BRCA 1 and/or 2 mutations or
2. have the high grade serous ovarian cancer subtype.

The data showed that olaparib reduced the risk of progression by 65% in all HGSOC patients and by ~80% in patients with the BRCA mutation. This is a terrific result and is impressive especially for a single drug that is fairly well tolerated.

Importantly Olaparib Worked Well in All Patients But Slightly Better in BRCA+ Mutants

At ASCO on Saturday, June 1st, updated results from the Ledermann study will be presented. Since that initial data, all patients were followed-up to ascertain their BRCA mutation status. The data will show that 136 of the 265 patients had the BRCA mutation.

Olaparib worked in all high grade serous ovarian cancer patients but showed slightly better outcomes in BRCAmut.

Interestingly, olaparib worked very well in patients who were BRCA + and in those who were BRCA -. Admittedly, olaparib worked better in patients who had the BRCA mutation relative to those who did not have the mutation, but that benefit was incremental as there was clear benefit in everyone.

This makes sense since it is thought that the homologous recombination defect (HRD) is prevalent in patients with HGSOC who are sensitive to platinum therapy.

Olaparib Shows Overall Survival Trend in BRCA+ Patients

In a subset of patients with BRCA mutations (both germ-line and somatic), olaparib showed an OS trend of 34.9 months for olaparib vs. 31.4 months for placebo (HR 0.74) (Figure 16).

Figure 16. Olaparib Works in All High Grade Serous Ovarian Cancer Patients and Also in BOTH Germ-Line and Somatic Mutations

Olaparib works in all BRCA mutations

	BRCA Mutation Status	Olaparib Dose	n	PFS (Mos)	HR (PFS) (p value)	Overall Survival (Mos)	HR (OS) (p value)
Germ-line + somatic	BRCAm (Germ-line, n=96 + somatic, n=40)	400mg BID	136	11.2	0.19 (p<0.0001)	34.9	0.74 (not sign)
		Placebo	122	4.3		31.9	
Germ-line alone	gBRCAm	400mg BID	96	11.2	0.17 (p<0.001)		0.85 (not sign)
	gBRCAwt	Placebo	122	4.1			0.84 (not sign)
All patients	All	400mg BID	136	8.4	p<0.001 (HR 0.35)	29.8	0.88 (not sign)
	All	Placebo	129	4.8		27.8	

Olaparib works in all patients regardless of BRCA status

Source: Ledermann et al & Citi Research

Olaparib Looks On Par With BioMarin's BMN-673

While it has been common wisdom to believe that BioMarin's BMN-673 is likely the most potent PARP inhibitor in clinical studies, the clinical data thus far shows that olaparib has equal potency based on overall response rates.

Figure 17. Olaparib in BRCA + Patients

n	Cancer	ORR (RECIST and/or CA-125)
193	Ovarian	31%
62	Breast	13%

Source: ASCO 2013

The data with olaparib is highly variable across studies. So it is very tough to compare it to BMN-673's and niraparib's small data thus far.

What is confusing is that some sets of data report overall response rates (ORR) just based on the stringent RECIST criteria that only looks at tumor shrinkage by radiography while other data also includes the CA-125 blood marker (less stringent).

When we compare olaparib's ORR including RECIST + CA-125, we see that olaparib has equal potency to BMN-673 and slightly better potency than niraparib in small studies. This puts the drug on apples-to-apples comparison to BioMarin's BMN-673 and Tesaro's niraparib (Figure 18).

But when we evaluate olaparib's response rates in a sizable recent study in 193 BRCA + ovarian cancer patients, the data is far less robust (Figure 17). This data will be shown at ASCO 2013.

It is possible that the difference has to do with the widely different sample sizes across all these studies.

Figure 18. Olaparib Data in Ovarian Cancer

Study	# of Patients	Treatment	Mutation Status	Median PFS (Mos)	ORR (RECIST)	ORR (RECIST + CA-125)	Duration of Response (mos)	P value (HR)
Kaye	**32**	Olaparib 400mg BID	BRCA +	8.8	31%	59%	6.0	Not sign (HR: 0.88)
	32	Olaparib 200mg BID	BRCA +	6.5	25%	38%	6.8	
	33	PEG-Doxil (PLD 50mg/m2)	BRCA +	7.1	18%	39%	5.5	
Ledermann (NEJM 2012)	**136**	**Olaparib 400mg BID**	**All**	**8.4**	**12%**	**13%**		**p<0.001 (HR 0.35)**
	129	**Placebo**	**All**	**4.8**	**4%**	**6%**		
Fong (NEJM)	**6**	Olaparib 200mg BID	BRCA +		50%	50%		
	4	Olaparib 400mg BID	BRCA +		100%	100%		
Fong (JCO)	**13 Platinum Sensitive**	Olaparib 200mg BID	BRCA +		46%	62%	~7	
	24 Platinum Resistant	Olaparib 200mg BID	BRCA +		34%	42%	~7	
	13 Platinum Refractory	Olaparib 200mg BID	BRCA +		0%	15%		
Audeh	**33**	Olaparib 400mg BID	BRCA +	5.8	33% (6% CR, 27% PR) Plat sensitive: 38% Plat resistant: 30%	---	9.7	
	24	Olaparib 100mg BID	BRCA +	1.9	13% PR Plat sensitive: 50%	---	9.0	
Gelmon	**17**	Olaparib 400mg BID	BRCA +	7.4	41% PR	76% (13/17)	5.2	
	46	Olaparib 400mg BID	BRCA -	6.4	24% PR	30% (10/38)		

Source: Medical Literature & Citi Research

Platinum Sensitivity Is Correlated With Response to PARP Inhibitors

Based on data from several studies, it has been shown that platinum sensitivity is a better predictor of response to a PARP inhibitor than BRCA status.

Figure 19. Olaparib Activity By Platinum Sensitivity Status in Ovarian Cancer

n	Platinum Status	Olaparib Dose	ORR (CR/PR) (By RECIST)	ORR (By RECIST + CA-125)
13	Sensitive	200mg BID	46%	62%
24	Resistant	200mg BID	34%	42%
15	Refractory	200mg BID	0%	15%

Source: Fong et al, JCO

Figure 20. Olaparib Activity By Platinum Sensitivity & BRCA Status in Ovarian Cancer

n	Platinum Status	Olaparib Dose	ORR (CR/PR) (By RECIST)	
			BRCA +	BRCA -
25	Sensitive	400mg BID	60% (3/5)	50% (10/20)
38	Resistant	400mg BID	33% (4/12)	4% (1/26)
15	Refractory	400mg BID	18% (2/11)	17% (4/23)

Source: Gelmon et al, Lancet

This helps explain why future studies with PARP inhibitors will enroll high grade serous ovarian cancer (HGSOC) patients who are still sensitive to platinum therapy.

Figure 21. Platinum Sensitivity and Olaparib Response

Germline BRCA status	Response to prior platinum	RECIST response to olaparib
BRCA mutation positive	Platinum sensitive	6/13 (46%)
	Platinum resistant	8/24 (33%)
BRCA mutation negative	Platinum sensitive	10/20 (50%)
	Platinum resistant	1/28 (4%)

Source: Fong et al, JCO, and Oza et al, 2010

AstraZeneca Will File For Approval in EU-Will Start Ph 3 in U.S. Soon

As a result of the Ledermann data, the European Medicines Agency encouraged AstraZeneca to file for accelerated approval based on these phase 2 results. We anticipate that AstraZeneca will file in H2:13 and will be approved in H2:14 in Europe for BRCAmut patients.

In the U.S., the FDA is unlikely to accept this data since the study did not stratify by BRCA status at baseline and did not validate a diagnostic test as part of the therapeutic strategy in the study.

As a result, we anticipate that AstraZeneca will require data from the OSTRIA1 phase 3 study to support approval.

Ph 3 Plans for Olaparib in Ovarian, Breast and Gastric Cancers

Astra Zeneca is planning to start ph 3 trials in ovarian and breast cancers by the end of 2013. We anticipate that ph 3 plans for olaparib + chemo for gastric cancer are also underway and could start in 2013.

Ph 3 OSTRIA1 Study in Ovarian Cancer Will Start Soon

AstraZeneca will initiate soon the ph 3 OSTRIA1 study testing olaparib as monotherapy maintenance in high grade serous BRCA+ ovarian cancer patients who have had a response to prior first line platinum therapy.

The study will enroll 344 patients and will likely include both germ-line and somatic BRCA mutations. The initial data collection is expected in July 2016. We expect approval in 2017 in the U.S. based on this study.

- **Primary endpoint:** PFS.
- **Secondary endpoints:** overall survival, response rates, and affect of BRCA mutation status on PFS.

Each Company is Adopting a Different Ph 3 Strategy

AstraZeneca will randomize patients who are known to be HGSOC who also have the BRCA mutations. Both germ-line and somatic mutations will likely be included in the study (see figures 22-23).

Tesaro will enroll patients who have either HGSOC or are unknown to have BRCA mutation. The study will only enroll germ-line BRCA. The study will be randomized to test the activity of niraparib in BRCA mutants and BRCA non-mutants separately.

Clovis Oncology will enroll patients who have either germ-line and/or somatic mutations, other non BRCA HRD mutations, or HGSOC. Thus, it will prospectively evaluate the activity in all 3 segments (please see subsequent sections for discussion of this strategy).

Figure 22. HGSOC Ph 3 Trial Designs

AstraZeneca and Tesaro will test HGSOC vs BRCA mutants without stratifying by germ-line vs somatic BRCA mutations

Company	Drug	HGSOC	Germ-line	Somatic	Non BRCA HRD
AstraZeneca	Olaparib	√	√	√	
Tesaro	Niraparib	√	√		
Clovis	Rucaparib	√	√	√	√

Clovis will test HGSOC vs germ-line vs somatic BRCA mutations

Source: Citi Research and company filings

Figure 23. Ph 3 HGSOC Strategy

Company	Strategy
AstraZeneca	Might include both gBRCAmut and sBRCAmut
Tesaro	Will randomize gBRCAmut vs non-gBRCAmut (ie will not evaluate somatic BRCAmut)
Clovis	Will randomize gBRCAmut vs sBRCAmut vs non-BRCAmut

Source: Citi Research and company filings

Olaparib's Tablet Formulation Will Be Used in the Ph 3 Study

AstraZeneca initially used a capsule formulation for olaparib which required 16 pills per day. Since then, the company has reformulated into a tablet formulation that will required 4 tablets per day (2 tabs twice daily).

Olaparib's Tablet Formulation Has More Predictable Exposure Levels

AstraZeneca has published results from a PK/PD study showing that olaparib's tablets at doses of 300mg BID and above are comparable to or better than the 400mg capsule formulation in terms of steady state peak, trough plasma concentration, and bioequivalence.

Importantly, there was less inter-patient variability in the steady state exposure levels with the tablet formulation (~3-4 fold) compared to capsule formulation (~8

fold). This should help ensuring that all patients have similar levels of the drug in their circulation.

Figure 24. Olaparib Exposure Level Comparison of Capsule and Tablet Formulation

PK parameter*, day 29	Olaparib dose				
	DE1		DE2		
	200 mg tablet (n=11)	400 mg capsule (n=10)	300 mg tablet (n=15)	400 mg tablet (n=13)	400 mg capsule (n=18)
$C_{max, ss}$	6.88 (4.01–10.4)	5.71 (2.38–10.9)	9.28 (2.28–14.7)	12.0 (8.45–16.9)	6.15 (3.50–13.3)
AUC_{ss}	36.1 (16.0–69.0)	43.1 (18.1–98.6)	57.5 (23.1–96.0)	70.3 (44.8–106)	39.8 (18.7–147)
$C_{min, ss}$	1.00 (0.28–3.10)	1.86 (0.53–6.67)	1.81 (0.34–3.83)	1.98 (0.76–3.61)	0.97 (0.23–8.49)

*Geometric mean (range)

Source: Molife et al., ASCO 2012

Olaparib's Tablet Formulation Response Rate Similar to Capsule

In terms of response rates, the 300mg BID tablet formulation showed comparable response rates to the 400mg BID capsule formulation. This support using this dose in the phase 3 studies.

Figure 25. Efficacy of Tablet Formulation Compared to Capsule Formulation

Response status, n (%)	Olaparib dose				
	DE1		DE2		
	200 mg tablet (n=13)	400 mg capsule (n=11)	300 mg tablet (n=18)	400 mg tablet (n=17)	400 mg capsule (n=18)
Responders (confirmed)					
Complete response	0	0	0	0	0
Partial response	1 (8)	0	4 (22)	2 (12)	4 (22)
ORR	**1 (8)**	**0**	**4 (22)**	**2 (12)**	**4 (22)**
Non-responders					
Stable disease ≥8 weeks	5 (39)	9 (82)	10 (56)	10 (59)	11 (61)
Progressive disease	6 (46)	2 (18)	4 (22)	3 (18)	0
Not evaluable	1 (8)	0	0	2 (12)	3 (17)

Source: Molife et al., ASCO 2012

Olaparib Tablet Formulation Not as Effective in Tumor Shrinkage

Olaparib tablet formulation looks fine but seems to be slightly less potent and cause more hematologic toxicity than the capsule formulation. The benefit is much fewer pills (4 vs 16).

However, we found 2 small issues with the 300mg BID tablet formulation namely:

- that it causes more hematologic toxicities than the 400mg capsule and
- that the tumor shrinkage % was less than the 400mg capsule (recall that BMN-673 showed more potent and quicker tumor shrinkage than olaparib in animal models).

We view these as salient points that are worth highlighting, but it is not clear whether these will dramatically impact the chances that the OSTRIA1 study will be successful or will be detriments to olaparib's commercial potential vs competitive agents.

Figure 26. Comparison of Effect on Tumor Size by Tablet Formulation vs. Capsule Formulation

	Olaparib dose				
	DE1		DE2		
	200 mg tablet (n=13)	400 mg capsule (n=11)	300 mg tablet (n=18)	400 mg tablet (n=17)	400 mg capsule (n=18)
Unadjusted mean, (%)	4.0	−12.2	−8.3	−25.3	−19.3
LS mean, (%)	4.5	−12.8	−8.0	−25.5	−19.4
Treatment effect					
Difference in LS means	17.3		11.4*	−6.0*	
95% CI	−11.8, 46.3		−8.0, 30.7	−25.7, 13.6	
P value (1-sided)	*P*=0.12†		*P*=0.12	*P*=0.27	

Source: Molife et al., ASCO 2012

Tesaro's Niraparib in Ovarian Cancer Is the Best Way to Play the PARP Theme

Niraparib has been tested in ovarian cancer patients who are either gBRCA+ or are platinum sensitive or resistant. The data confirmed earlier results with olaparib and highlighted that PARP inhibitors are promising in gBRCA+ and platinum sensitive ovarian cancer. The overall response rates are mostly on par with those seen with olaparib and BMN-673. Interestingly, the duration of response was long at 11 months in these small patient groups (see Figure 27).

Figure 27. Niraparib Data in Ovarian Cancer By BRCA & Platinum Status

n	Ovarian Cancer	ORR (RECIST and/or CA-125)	Duration of Response (Mos)
20	gBRCA+	45% (9/20)	
	Platinum Sensitive	60%	14.3
	Platinum Resistant	33%	11.3
3	Somatic BRCA + Platinum Sensitive	66% (2/3)	
20	Somatic BRCA + Platinum Resistant	15% (3/20)	

Source: ASCO 2013

Niraparib Phase 3 Study Will Begin in Mid-'13 – Data in H1:16

Powering assumptions for the niraparib phase 3 trial were based on the phase 2 results published in the New England Journal of Medicine (NEJM) by Ledermann for olaparib (see Figure 18).

Niraparib is also quickly advancing towards starting its phase 3 study in HGSOC or gBRCAmut platinum-sensitive ovarian cancer patients. The study will be a global randomized study that should start in mid-'13. We expect the initial data collection in March 2016.

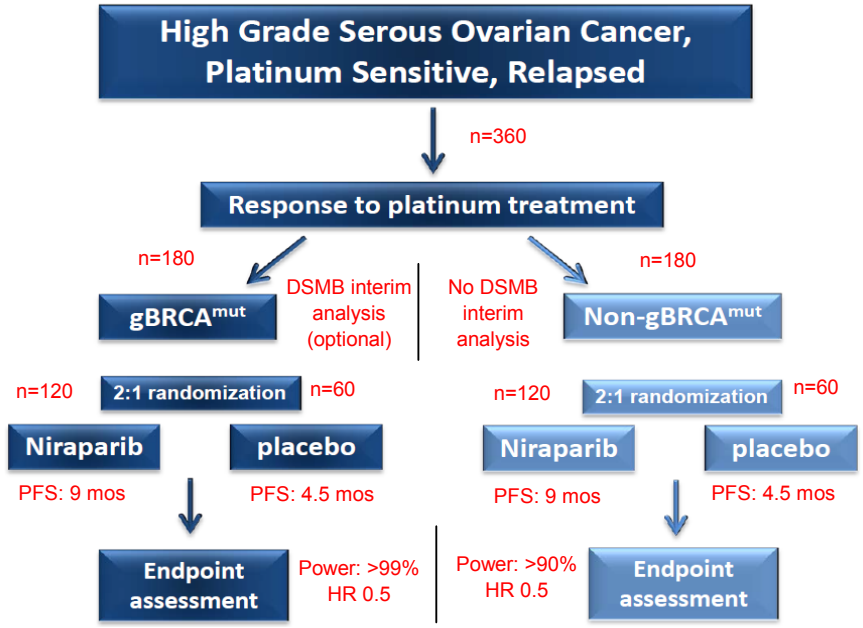
The trial will enroll ~360 patients who have progressed following 2nd-line platinum-based therapy, divided into two cohorts of germ-line BRCA+ and non-BRCAmut (ie HGSOC unselected). In each cohort, patients will be randomized 2:1 to receive either niraparib or placebo.

Olaparib showed an 8.4 mos PFS in all HGSOC patients and ~11 mos PFS benefit in BRCAmut.

Tesaro powered their study to show a 9 mos PFS in BRCAmut or HGSOC.

In our model, we assume only a 7 mos PFS to be conservative and leave room in case the ph 3 shows the typical efficacy step down from ph 2.

Figure 28. Niraparib Phase 3 Ovarian Cancer Trial Design



Source: Tesaro and Citi Research

The Study is Highly Powered For Success

The **primary endpoint** of the phase 3 for both cohorts of the study is progression free survival (PFS). **Secondary endpoints** include overall survival, PFS Two, and diagnostic test criteria.

Each arm has a 90% power to detect a hazard ratio of 0.50 with p<0.05 assuming a median PFS of 4.5 months in the control group vs. 9 months on niraparib. But the study has plenty of power to deter a HR <0.7.

BioMarin's BMN-673 is Also Promising – Update at ASCO

Preliminary data from a ph 1/2 dose-escalation study in 17 gBRCA+ ovarian cancer patients will be presented at ASCO. The abstract shows that 11/17 or 65% of patients achieved a response as noted by RECIST and/or CA-125. BioMarin has noted that these included at least 1 CR.

At ASCO, BioMarin will present the full data including 11 additional gBRCA+ women from the 1mg dose expansion cohort. We anticipate that the final data will be more robust given that the initial data included the low dose cohort of BMN-673 (see Figure 29).

Figure 29. BMN-673 Activity in Ovarian Cancer

n	Cancer	BMN-673 Dose	ORR (By RECIST and/or CA-125)
17	Ovarian	25-1,100 ug/d	65% (RECIST and/or CA-125)
6	Breast	25-1,100 ug/d	33% (RECIST)

Source: ASCO 2013

BioMarin Will Not Advance BMN-673 to Ph 3 in Ovarian Cancer

At this point, BioMarin does not intend on moving BMN-673 towards phase 3 studies in ovarian cancer as the company feels that this opportunity will take too long to get to market and is too competitive. Also, BioMarin feels that it might be tough to show an overall survival benefit in ovarian cancer since patients can receive platinum agent after the PARP inhibitor and this will confound the study.

Clovis' Rucaparib Is Slightly Behind – More Complex Development Path Ahead

Rucaparib is an orally bioavailable, small molecule inhibitor of PARP-1/2 mutations. Clovis has in-licensed the drug from Pfizer and has re-formulated it from IV to oral. The oral bioavailability is 35-40% of the IV.

Rucaparib is a little behind the other PARPs as Clovis is now completing its dose escalation phase 1/2 study.

Clovis is working closely with Foundation Medicine to develop a companion diagnostic test to identify a broader set of HRD mutations that can be targeted by rucaparib.

How Does Rucaparib Data Compare? Hard to Tell As It is Still Dose Escalating

At ASCO, Clovis will release data from the phase 1/2 dose escalation study. The study is still ongoing and now testing 480mg BID.

Based on the interim data with doses as high as 240mg BID, 2 of 24 breast and ovarian cancer patients achieved a PR (both were BRCAmut). The study is still ongoing and updated results will be presented at ASCO.

Next Steps for Rucaparib – 2 Studies Are Planned

Clovis will initiate two additional studies to explore:

- Ph 2 study to validate a diagnostic test in collaboration with Foundation Medicine and plans to use this test in the phase 3 analysis
- Conduct a phase 3 study to support global approval.

Phase 2 Diagnostic Study Will Start in Q3:13

The benefit of Clovis' companion diagnostic is that it will differentiate rucaparib over the competition and could open the non-BRCA HRD segment (~30% of HGSOC patients).

The drawbacks are that it will delay rucaparib's approval and might not be unnecessary if PARP inhibitors work in all HGSOC patients.

Clovis plans to conduct a study in 200 recurrent platinum sensitive ovarian cancer women with BRCA mutation. Of those, ~50 will have the de novo germ-line and somatic BRCA mutations (who have not been diagnosed previously). The study will attempt to enroll non-BRCA HRD ovarian cancer patients to define the associated gene signature that might benefit from rucaparib.

The purpose of the study is to validate Foundation Medicine's tissue-based diagnostic to help differentiate rucaparib in the marketplace by having its own validated diagnostic test.

Phase 3 Study Will Start in Q4:13 – Date in H1:17 – Approval in 2018

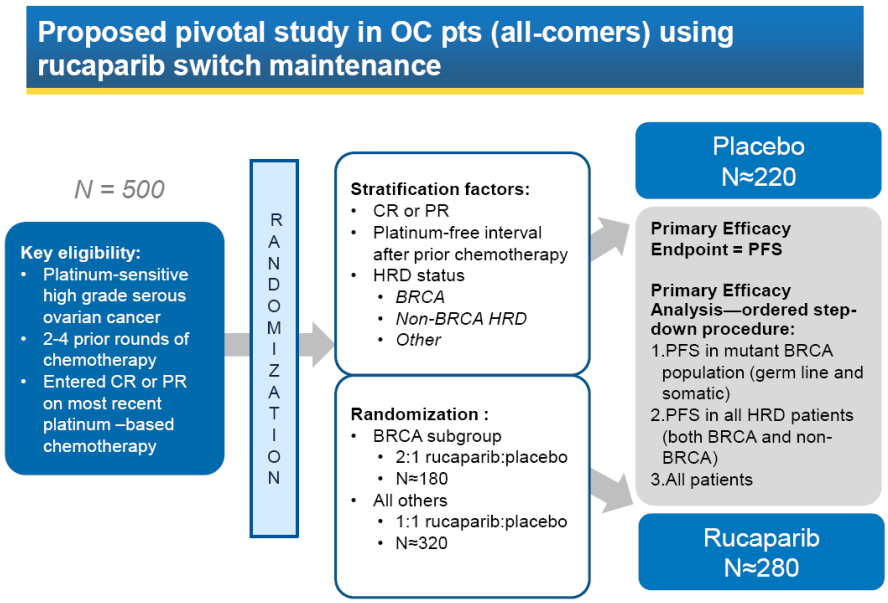
Clovis plans to start a global registration study in platinum-sensitive, high grade ovarian cancer with efficacy analysis pre-specified in populations defined by deficiencies in BRCA and other DNA repair genes (aka HRD mutations).

Clovis has an agreement with Foundation Medicine to identify additional genetic markers beyond BRCA which are involved in DNA repair, which could be used to identify patients who could benefit from PARP inhibition. This should help expand the patients who could be treated with PARP inhibitors from 15% of ovarian cancer patients who have germ-line BRCA mutations to 40%-50% of patients who have somatic BRCA and 25 HRD genetic mutations.

This phase 3 study will specifically evaluate the activity of rucaparib vs placebo in patients who are BRCA mutant (germ-line and somatic), non-BRCA HRD, and high grade serous ovarian without any mutations.

Clovis will have data in 2015 from the ph 2 diagnostic test study and will use that information to lock down the statistical plans to use to analyzing its phase 3 results in 2017.

Figure 30. Rucaparib's Phase 3 HGS Ovarian Cancer Study Design



Source: Clovis Oncology

Does Clovis' Strategy Make Sense?

Clovis' strategy is conceptually sound, in our view. We like the concept of developing a diagnostic to go along with the drug to ascertain which patients benefit the most. We especially like the concept of testing rucaparib prospectively in HRD mutants (non BRCA) to expand the addressable patient population.

However, the big catch is that technically all patients have benefited from olaparib in the Ledermann study and the data with PARPs has consistently shown that HGSOC platinum-sensitive status is a solid predictor of response. We admit that BRCAmut patients derived more of a PFS benefit and even had a positive overall survival trend.

But the difference was small and the data showed that PARP inhibitors are very attractive for all patients given their single agent activity without overwhelming toxicity.

Rucaparib Likely Approved a Year Later Than Olaparib and Niraparib

In Europe, we anticipate that olaparib will be approved in H2:14 for gBRCA+ patients. In the U.S., both Tesaro and AstraZeneca will start their phase 3 studies 3-6 months earlier than Clovis and will have ~1/3 fewer patients. Thus, we anticipate that Clovis could get to the market in 2018 vs 2017 for the competition.

Clovis' Strategy is Differentiated But Risky – Might Not Need a New Diagnostic Test

Unless there is a clear need for a new diagnostic test that is specific for both BRCAmut and non-BRCA HRD mutations, this strategy might unnecessarily delay rucaparib. In our view, it all depends on the magnitude of the benefit for selected vs unselected HGSOC patients.

Conversely, if there is a meaningful difference between patients with mutations vs HGSOC without mutations, then Clovis' strategy will be very successful and could drive rucaparib to at least dominate the HRD segment (~30% of patients) that is not specifically targeted by AstraZeneca or Tesaro.

Our Model Assumptions For the Ovarian Cancer Market

At this stage, it is very tough to call a winner among the 3 PARP inhibitors. However, there are considerable differences in time to market.

We anticipate that olaparib will be approved in Europe in late 2014 and will have a first mover advantage. We anticipate approval in the U.S. in 2017. Olaparib should initially dominate the European market and will likely then cede share to niraparib due to its BID vs QD dosing.

We model that niraparib will be approved in the US/EU in 2017. In the US, we anticipate that the 2 drugs will split the market equally. In Europe, we anticipate that niraparib will capture some share from olaparib driven by its once daily dosing.

As rucaparib is behind, we model approval in 2018. At this point, we are not convinced that rucaparib's strategy will provide ample differentiation over olaparib and niraparib as all drugs should be successful in the broader HGSOC segment. Thus, rucaparib should capture some share but will remain the 3rd player in this segment as it will be late to market and will carry twice daily dosing.

We anticipate that the average treatment duration will be 7 months at a cost of $15k/monts in the US and $12.5k/month in Europe.

Figure 31. U.S Market Model for PARP Inhibitors in Ovarian Cancer

	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E
U.S Women Population (000's)	**173,341**	**176,807**	**180,344**	**183,951**	**187,630**	**191,382**	**195,210**	**199,114**	**203,096**	**207,158**	**211,301**
Incidence of Ovarian Cancer (12.5 per 100,000 Women)	**21,668**	**22,101**	**22,543**	**22,994**	**23,454**	**23,923**	**24,401**	**24,889**	**25,387**	**25,895**	**26,413**
Prevalence of Ovarian Cancer	97,258	95,045	93,826	93,364	93,476	94,030	94,924	96,082	97,449	98,981	100,649
% Diagnosed	*14%*	*14%*	*14%*	*14%*	*14%*	*14%*	*14%*	*14%*	*14%*	*14%*	*14%*
Diagnosed Ovarian Cancer Patients	24,268	24,753	25,248	25,753	26,268	26,793	27,329	27,876	28,433	29,002	29,582
% High Grade Serous	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%
High-Grade Serous Ovarian Cancer patients diagnosed and treated (all ty	16,987	17,327	17,674	18,027	18,388	18,755	19,131	19,513	19,903	20,302	20,708
% Metastatic	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*
Metastatic Patients Diagnosed and Treated (all types)	15,289	15,594	15,906	16,224	16,549	16,880	17,218	17,562	17,913	18,271	18,637
% Platinum Sensitive	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
Platinum Sensitive Patients Diagnosed and Treated (all types) (000s)	10,702	10,916	11,134	11,357	11,584	11,816	12,052	12,293	12,539	12,790	13,046
% Olaparib Penetration	10%	20%	20%	25%	25%	25%	25%	25%	25%	25%	25%
Patients treated with Olaparib (000s)	1,049	2,140	2,183	2,784	2,839	2,896	2,954	3,013	3,073	3,135	3,197
# Mos on therapy	7	7	7	7	7	7	7	7	7	7	7
Price (month)	$15,000	$15,450	$15,914	$16,391	$16,883	$17,389	$17,911	$18,448	$19,002	$19,572	$20,159
Olaparib Price per patient per year (7 months PFS)	$105,000	$108,150	$111,395	$114,736	$118,178	$121,724	$125,375	$129,137	$133,011	$137,001	$141,111
Olaparib sales ($M)	**$110**	**$231**	**$243**	**$319**	**$336**	**$353**	**$370**	**$389**	**$409**	**$429**	**$451**
Probabilty Adjusted Olaparib sales ($M)	**$72**	**$150**	**$158**	**$208**	**$218**	**$229**	**$241**	**$253**	**$266**	**$279**	**$293**
% Niraparib Penetration	10%	20%	20%	25%	25%	25%	25%	25%	25%	25%	25%
Patients treated with Niraparib (000s)	1,070	2,183	2,227	2,839	2,896	2,954	3,013	3,073	3,135	3,197	3,261
# Mos on therapy	7	7	7	7	7	7	7	7	7	7	7
Price (month)	$15,000	$15,450	$15,914	$16,391	$16,883	$17,389	$17,911	$18,448	$19,002	$19,572	$20,159
Niraparib Price per patient per year	$105,000	$110,250	$115,763	$121,551	$127,628	$134,010	$140,710	$147,746	$155,133	$162,889	$171,034
Niraparib sales (000s)	**$112**	**$241**	**$258**	**$345**	**$370**	**$396**	**$424**	**$454**	**$486**	**$521**	**$558**
Probabilty Adjusted Niraparib sales ($M)	**$73**	**$156**	**$168**	**$224**	**$240**	**$257**	**$276**	**$295**	**$316**	**$339**	**$363**
% Rucaparib Penetration		5%	15%	20%	20%	20%	20%	20%	20%	20%	20%
Patients treated with Rucaparib (000s)		546	1,670	2,271	2,317	2,363	2,410	2,459	2,508	2,558	2,609
# Mos on therapy		7	7	7	7	7	7	7	7	7	7
Price (month)		$15,450	$15,914	$16,391	$16,883	$17,389	$17,911	$18,448	$19,002	$19,572	$20,159
Niraparib Price per patient per year		$108,150	$111,395	$114,736	$118,178	$121,724	$125,375	$129,137	$133,011	$137,001	$141,111
Rucaparib sales (000s)		**$59**	**$186**	**$261**	**$274**	**$288**	**$302**	**$318**	**$334**	**$350**	**$368**
Probabilty Adjusted Rucaparib sales ($M)		**$38**	**$121**	**$169**	**$178**	**$187**	**$196**	**$206**	**$217**	**$228**	**$239**
U.S. Olaparib Sales	**$72**	**$150**	**$158**	**$208**	**$218**	**$229**	**$241**	**$253**	**$266**	**$279**	**$293**
U.S. Niraparib Sales	**$73**	**$156**	**$168**	**$224**	**$240**	**$257**	**$276**	**$295**	**$316**	**$339**	**$363**
U.S. Rucaparib Sales	**$0**	**$38**	**$121**	**$169**	**$178**	**$187**	**$196**	**$206**	**$217**	**$228**	**$239**
Total U.S. Ovarian Cancer Sales	**$145**	**$345**	**$447**	**$601**	**$636**	**$673**	**$713**	**$754**	**$799**	**$845**	**$895**
Global Olaparib Sales	**$344**	**$366**	**$315**	**$368**	**$382**	**$396**	**$411**	**$427**	**$443**	**$460**	**$478**
Global Niraparib Sales	**$103**	**$280**	**$325**	**$385**	**$404**	**$424**	**$446**	**$469**	**$493**	**$519**	**$547**
Global Rucaparib Sales	**$0**	**$100**	**$247**	**$298**	**$309**	**$321**	**$333**	**$345**	**$359**	**$372**	**$387**
Total Global Ovarian Cancer Sales	**$447**	**$746**	**$887**	**$1,051**	**$1,095**	**$1,141**	**$1,190**	**$1,241**	**$1,295**	**$1,352**	**$1,411**

Source: Citi Research

Figure 32. European Market Model for PARP Inhibitors in Ovarian Cancer

	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E
Europe Women Population (000's)	**172,303**	**175,749**	**179,264**	**182,849**	**186,506**	**190,236**	**194,041**	**197,922**	**201,880**	**205,918**
Incidence of Ovarian Cancer(12.6 per 100,000 Women)	**21,710**	**22,144**	**22,587**	**23,039**	**23,500**	**23,970**	**24,449**	**24,938**	**25,437**	**25,946**
Prevalence of Ovarian Cancer	247,540	256,070	264,573	273,061	281,542	290,027	298,525	307,044	315,594	324,182
% Diagnosed	*14%*	*14%*	*14%*	*14%*	*14%*	*14%*	*14%*	*14%*	*14%*	*14%*
Diagnosed Ovarian Cancer Patients	24,122	24,605	25,097	25,599	26,111	26,633	27,166	27,709	28,263	28,828
% high Grade Serous	70%	70%	70%	70%	70%	70%	70%	70%	70%	70%
High-grade Serous Ovarian Cancer patients diagnosed and treated (all types)	16,886	17,223	17,568	17,919	18,278	18,643	19,016	19,396	19,784	20,180
% Metastatic	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*	*90%*
Metastatic patients diagnosed and treated (all types)	15,197	15,501	15,811	16,127	16,450	16,779	17,114	17,457	17,806	18,162
% Platinum Sensitive	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
Platinum Sensitive Patients Diagnosed and Treated (all types) (000s)	10,638	10,851	11,068	11,289	11,515	11,745	11,980	12,220	12,464	12,713
% Olaparib Penetration	45%	35%	25%	25%	25%	25%	25%	25%	25%	25%
Patients treated with Olaparib	4,787	3,798	2,767	2,822	2,879	2,936	2,995	3,055	3,116	3,178
# Mos on therapy	7	7	7	7	7	7	7	7	7	7
Price (month)	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500
Olaparib Price per patient per year (7 months PFS)	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500
Olaparib sales ($M)	**$419**	**$332**	**$242**	**$247**	**$252**	**$257**	**$262**	**$267**	**$273**	**$278**
Probabilty Adjusted Olaparib sales ($M)	**$272**	**$216**	**$157**	**$161**	**$164**	**$167**	**$170**	**$174**	**$177**	**$181**
% Niraparib Penetration	5%	20%	25%	25%	25%	25%	25%	25%	25%	25%
Patients treated with Niraparib	532	2,170	2,767	2,822	2,879	2,936	2,995	3,055	3,116	3,178
# Mos on therapy	7	7	7	7	7	7	7	7	7	7
Price (month)	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500
Niraparib Price per patient per year	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500
Niraparib sales (000s)	**$47**	**$190**	**$242**	**$247**	**$252**	**$257**	**$262**	**$267**	**$273**	**$278**
Probabilty Adjusted Niraparib sales ($M)	**$30**	**$123**	**$157**	**$161**	**$164**	**$167**	**$170**	**$174**	**$177**	**$181**
% Rucaparib Penetration		10%	20%	20%	20%	20%	20%	20%	20%	20%
Patients treated with Rucaparib		1,085	2,214	2,258	2,303	2,349	2,396	2,444	2,493	2,543
# Mos on therapy	7	7	7	7	7	7	7	7	7	7
Price (month)	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500
Rucaparib Price per patient per year	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500	$87,500
Rucaparib sales (000s)		**$95**	**$194**	**$198**	**$202**	**$206**	**$210**	**$214**	**$218**	**$222**
Probabilty Adjusted Rucaparib sales ($M)		**$62**	**$126**	**$128**	**$131**	**$134**	**$136**	**$139**	**$142**	**$145**
European Olaparib Sales	**$272**	**$216**	**$157**	**$161**	**$164**	**$167**	**$170**	**$174**	**$177**	**$181**
European Niraparib Sales	**$30**	**$123**	**$157**	**$161**	**$164**	**$167**	**$170**	**$174**	**$177**	**$181**
European Rucaparib Sales	**$0**	**$62**	**$126**	**$128**	**$131**	**$134**	**$136**	**$139**	**$142**	**$145**
Total European Ovarian Cancer Sales	**$303**	**$401**	**$441**	**$449**	**$458**	**$468**	**$477**	**$486**	**$496**	**$506**

Source: Citi Research

PARP Inhibitors in Breast Cancer

- **PARP inhibitors have shown encouraging activity in BRCAmut metastatic breast cancer patients as single agents.**
- **This should help differentiate these drugs over the chemo current standard of care by virtue of superior potency and better tolerability.**
- **~8%-10% of breast cancer patients have the BRCA mutation.**
- **We anticipate that all 3 players (AstraZeneca, Tesaro and BioMarin) will get to market in 2017.**
- **At this point, it is hard to differentiate among the drugs and so we give them all equivalent market share. Olaparib is dose 2x/day while niraparib and BMN-673 are dose once daily.**
- **Clovis Oncology is not planning on focusing on breast cancer.**

Olaparib in Breast Cancer Showed Positive Data

AstraZeneca plans to advance olaparib into phase 3 studies in breast cancer.

In breast cancer, the experience with PARP inhibitors has been more limited than in ovarian cancer. Nevertheless, the data follows the science and shows that these drugs have promising single agent activities in BRCAmut patients.

In a proof of concept study in 54 BRCAmut breast cancer patients, olaparib showed a 41% response rate with 5.7 months PFS. Median duration of response of ~140 days.

In a separate study by Gelmon, there were many drop outs that led to a very short 3.6 months PFS and no response rate (see Figure 33).

Figure 33. Olaparib Activity in Breast Cancer

Study	# of Patients	Treatment	Mutation Status	Median PFS (Mos)	ORR (RECIST)	Duration of Response (mos)
Tutt	27	Olaparib 400mg BID	BRCA +	5.7	41% (4% CR, 37% PR)	4.8
	27	Olaparib 100mg BID	BRCA +	3.8	22% PR	4.7
Gelmon	10	Olaparib 400mg BID	BRCA +	3.6	0%	1.9
	16	Olaparib 400mg BID	BRCA -	1.8	0%	

Source: Citi Research & Lancet

Initial Data With PARP Inhibitors in Triple Negative Breast Cancer Was Disappointing – Triple Negative is Not a Good Surrogate

Recall that the initial data with PARPs in triple negative breast cancer was disappointing. It was initially thought that PARP inhibitors will have high activity in this segment.

But more recently, it became to be appreciated that only 50-60% of triple negative patients carry a BRCAmut. In addition, as BRCAmut patients only account for 10-20% of triple negative patients, this segment is not fitting for a PARP inhibitor unless it is enriched for BRCAmut.

Figure 34. Niraparib in Breast Cancer

n	Breast Cancer	ORR (RECIST)
4	BRCA+	50% (2/4)

Source: Citi Research

Niraparib Data at ASCO Shows Good Potency in Few Patients

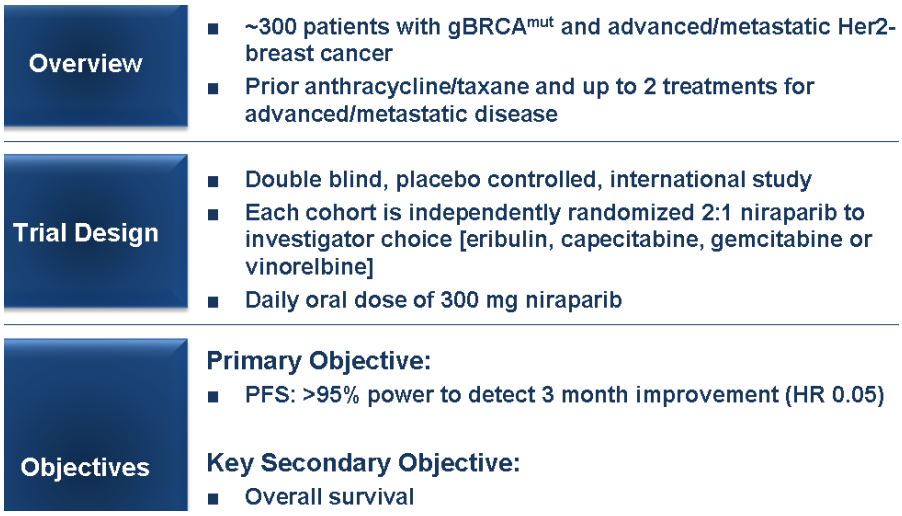
At ASCO, Tesaro will release data in 12 breast cancer patients who were in the dose escalation study. Of those, 4 patients were BRCA+ and 2/4 showed a response. We anticipate getting an update on the overall cohort at the conference.

Tesaro Moving to Phase 3 in Q4:13

Tesaro plans to start a 306 patients study in gBRCAmut advanced Her2- breast cancer patients. The study will test niraparib vs chemo (see Figure 35).

The study has a 99% power to detect a 6 mos PFS vs 3 mos for the control arm with a HR 0.5. The study even has ~100% power to detect a HR <0.69.

Figure 35. Niraparib Breast Cancer Ph3 Trial Design



Source: Tesaro

How Tesaro's Study is Powered?

The study is powered based on the assumption that the control arm will show ~2.5 months PFS in triple negative patients and 3.5 months in Her2- patients (see Figure 36).

The assumption of achieving 6 months of PFS in the niraparib arm is based on the 5.7 months achieved by olaparib (see Figure 33).

Figure 36. Chemo Data in 2nd-Line Breast Cancer

Second-Line									
Trial	**Arms**	**n**	**Prior Therpies**	**Response Rate**	**p-value**	**PFS (HR)**	**p-value**	**OS (HR)**	**p-value**
N/A	Docetaxel + Capecitabine 1250 mg/m^2 bid	255	Taxanes (10%), Anthracyclines (100%)	32.0%	0.025	TTP 6.2 mos (HR: 0.643)	0.0001	14.5 mos (HR: 0.775)	0.775
	Docetaxel	256		22.0%		**TTP 4.3 mos**		11.5 mos	
AVF2119g	Capecitabine + Avastin 15mg/kg q3w	232	Taxanes (100%), Anthracyclines (100%), Chemotherapy (100%)	19.8%	0.001	4.9 mos (HR: 0.98)	0.857	15.1 mos	NS
	Capecitabine	230		9.1%		**4.2 mos**		14.5 mos	
EMBRACE	Halaven 1.4 mg/m^2 (day 1+8)	508	Taxanes (99%), Anthracyclines (99%), Capecitabine (73%)	12.0%	0.002	3.7 mos (HR: 0.87)	0.137	13.1 mos (HR: 0.81)	0.041
	Treatment of physicains' choice	254		5.0%		**2.2 mos**		10.6 mos	
N/A	Gemzar + Paclitaxel	267	Prior Taxanes or Gemcitabine not allowed, Anthracyclines (96%), Chemotherapy (100%)	40.8%	<0.0001	TTP 5.2 mos (HR: 0.65)	<0.0001	18.6 mos (HR: 0.86)	NS
	Paclitaxel	262		22.1%		**TTP 2.9 mos**		15.8 mos	
RIBBON-2	Chemo† + Avastin 15mg/kg q3w	459	Anthracyclines and Taxane (46%), Chemotherapy (100%)	39.5%	0.0193	7.2 mos (HR: 0.78)	0.0072	18.0 mos (HR: 0.90)	NS
	Chemo†	225		29.6%		**5.1 mos**		16.4 mos	
GEICAM	Gemcitabine 1200 mg/m^2 + Vinorelbine 30 mg/m^2 (days 1+8)	125	Taxanes (100%), Anthracyclines (100%)	36.0%	NS	6.0 mos (HR: 0.66)	0.0028	15.9 mos	NS
	Vinorelbine 30 mg/m2	126		26.0%		**4.0 mos**		16.4 mos (HR: 0.80)	
SOLTI-0701	Sorafenib 400mg bid + Capecitabine 1000 mg/m2 bid	115	Taxanes (40%), Anthracyclines (86%)	NA	NA	4.3 mos (HR: 0.60)	0.001	22.2 mos (HR:0.86)	NS
	Capecitabine 1000 mg/m2 bid	114		NA		**2.5 mos**		20.9 mos	
N/A	Ixabepilone 40 mg/m^2 + Capecitabine 1250 mg/m^2	609	Taxanes (100%), Anthracyclines (100%)	43.3%	<0.0001	6.2 mos (HR: 0.79)	0.00005	16.4 (HR: 0.90)	0.0231
	Capecitabine 2500 mg/m^2	612		28.8%		**4.4 mos**		15.6	
AC01B07	Sorafenib 400 mg BID + Gemcitabine 1000 mg/m^2 or Capecitabine1000 mg/m^2	81	Taxanes (64%), Anthracyclines (3%), Chemotherapy (96%)	NA	NA	3.1 mos (HR: 0.57)	NA	NA	NA
	Gemcitabine 1000 mg/m2 or Capecitabine1000 mg/m2	79				**2.6 mos**			

*anthracycline-based combo, taxane [docetaxel or abraxane] or capecitabine
†paclitaxel wkly or q3w, abraxane q3, docetaxel q3, vinorelbine wkly, capecitabine or gemcitabine

Source: Citi Research and medical literature

Figure 37. BMN-673 in Breast Cancer

n	Cancer	BMN-673 Dose	ORR (By RECIST)
6	Breast	25-1,100 ug/d	33% (RECIST)

Source: ASCO 2013

BMN-673 Data at ASCO Will Showcase Its Efficacy

At ASCO, BioMarin will present data from 18 gBRCAmut breast cancer patients, including six patients from the dose escalation cohort at doses ranging from 25 µg to 1,100 µg and twelve patients from the dose expansion cohort at a dose of 1.0 mg.

Preliminary data from 4 patients showed a 33% response rate during the dose escalation phase.

BMN-673 Looks to Have Similar Potency to Olaparib

When we compare BMN-673's data vs olaparib, the drugs look fairly comparable. As a result, we do not anticipate that data at ASCO in additional 12 patients will look that different from earlier responses.

It is possible that the data might look slightly better but probably unlikely to be dramatically different.

BioMarin Plans to Start Phase 3 Studies in Q4:13

BioMarin has decided to advance BMN-673 into phase 3 studies in BRCA+ breast cancer patients who have gotten 0-2 prior lines of chemo. This is because the drug's solid potency and good tolerability can be very competitive with current available options (see Figure 36).

This have a high degree of confidence that this type of study could beat chemo and will offer a clear edge by virtue of better efficacy with a preferable tolerability profile.

AbbVie Targeting Veliparib for Combo Therapy in Breast Cancer

AbbVie will show data in BRCAmut breast cancer patients testing veliparib and carboplatin. As veliparib is not potent enough as a single agent, AbbVie has been focusing on a combo approach with chemo. The data shows that there was a solid response rate, but it also came at considerable toxicity. In addition, since there was no carboplatin control, it was tough to ascertain the benefit provided by veliparib directly.

Figure 38. Veliparib+Carboplatin in BRCA+ Breast Cancer

n	Breast Cancer	PFS (Mos)	Clinical Benefit Rate	Response Rate
26	BRCA+	7.8	75%	CR=12% PR=35%

Source: Citi Research and ASCO 2013

Our Model Assumptions For the Breast Cancer Market

At this stage, it is very tough to call a winner among the 3 PARP inhibitors. We anticipate that they will all be approved in breast cancer in 2017 and are splitting the market equally among the 3 drugs.

We anticipate that the average treatment duration will be 6 months at a cost of $15k/monts in the US and $12.5k/month in Europe.

Figure 39. U.S Market Model for PARP Inhibitors in Breast Cancer

	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E
Incidence Breast Cancer (U.S.)	241,420	243,834	246,273	248,735	251,223	253,735	256,272	258,835	261,423	264,037	266,678	269,345	272,038	274,758	277,506
% Local Disease	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*
Local Disease Patients	154,509	156,054	157,614	159,191	160,782	162,390	164,014	165,654	167,311	168,984	170,674	172,381	174,104	175,845	177,604
% Regional Disease	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*
Regional Disease Patients	67,598	68,274	68,956	69,646	70,342	71,046	71,756	72,474	73,199	73,930	74,670	75,417	76,171	76,932	77,702
% Metastatic	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*
Metastatic Disease Patients	19,314	19,507	19,702	19,899	20,098	20,299	20,502	20,707	20,914	21,123	21,334	21,548	21,763	21,981	22,200
Surgical Candiates Patients	201,827	203,845	205,884	207,943	210,022	212,122	214,244	216,386	218,550	220,735	222,943	225,172	227,424	229,698	231,995
% Surgical Candidates that Relapse	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
Surgical Candidates that Relapse	40,365	40,769	41,177	41,589	42,004	42,424	42,849	43,277	43,710	44,147	44,589	45,034	45,485	45,940	46,399
Treatment Options															
Adjuvant Therapy Candidates	201,827	203,845	205,884	207,943	210,022	212,122	214,244	216,386	218,550	220,735	222,943	225,172	227,424	229,698	231,995
First Line Therapy Candidates	59,679	80,758	81,565	82,381	83,205	84,037	84,877	85,726	86,583	87,449	88,324	89,207	90,099	91,000	91,910
% Moving to 2nd-line therapy	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Second-Line Therapy Candidates	29,840	40,379	40,783	41,191	41,602	42,018	42,439	42,863	43,292	43,725	44,162	44,603	45,050	45,500	45,955
% BRCA Positve Eligible for PARP Inhibitors	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
PARP Inhibitor Treated BRCA Patients	8,952	12,114	12,235	12,357	12,481	12,606	12,732	12,859	12,988	13,117	13,249	13,381	13,515	13,650	13,787
% Olaparib Penetration	10%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Patients treated with Olaparib	895	3,028	3,059	3,089	3,120	3,151	3,183	3,215	3,247	3,279	3,312	3,345	3,379	3,413	3,447
# Mos on therapy	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Price (month)	$15,000	$15,450	$15,914	$16,391	$16,883	$17,389	$17,911	$18,448	$19,002	$19,572	$20,159	$20,764	$21,386	$22,028	$22,689
Olaparib Price per patient per year (7 months PFS)	$90,000	$92,700	$95,481	$98,345	$101,296	$104,335	$107,465	$110,689	$114,009	$117,430	$120,952	$124,581	$128,318	$132,168	$136,133
Olaparib sales ($M)	**$81**	**$281**	**$292**	**$304**	**$316**	**$329**	**$342**	**$356**	**$370**	**$385**	**$401**	**$417**	**$434**	**$451**	**$469**
Probabilty Adjusted Olaparib sales ($M)	**$48**	**$168**	**$175**	**$182**	**$190**	**$197**	**$205**	**$214**	**$222**	**$231**	**$240**	**$250**	**$260**	**$271**	**$282**
% Niraparib Penetration	10%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Patients treated with Niraparib	895	3,028	3,059	3,089	3,120	3,151	3,183	3,215	3,247	3,279	3,312	3,345	3,379	3,413	3,447
# Mos on therapy	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Price (month)	$15,000	$15,450	$15,914	$16,391	$16,883	$17,389	$17,911	$18,448	$19,002	$19,572	$20,159	$20,764	$21,386	$22,028	$22,689
Niraparib Price per patient per year	$90,000	$92,700	$95,481	$98,345	$101,296	$104,335	$107,465	$110,689	$114,009	$117,430	$120,952	$124,581	$128,318	$132,168	$136,133
Niraparib sales ($M)	**$81**	**$281**	**$292**	**$304**	**$316**	**$329**	**$342**	**$356**	**$370**	**$385**	**$401**	**$417**	**$434**	**$451**	**$469**
Probabilty Adjusted Niraparib sales ($M)	**$48**	**$168**	**$175**	**$182**	**$190**	**$197**	**$205**	**$214**	**$222**	**$231**	**$240**	**$250**	**$260**	**$271**	**$282**
% BMN-673 Penetration	10%	20%	20%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Patients treated with BMN-673	895	2,423	2,447	3,089	3,120	3,151	3,183	3,215	3,247	3,279	3,312	3,345	3,379	3,413	3,447
# Mos on therapy	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Price (month)	$15,000	$15,450	$15,914	$16,391	$16,883	$17,389	$17,911	$18,448	$19,002	$19,572	$20,159	$20,764	$21,386	$22,028	$22,689
BMN-673 Price per patient per year	$90,000	$92,700	$95,481	$98,345	$101,296	$104,335	$107,465	$110,689	$114,009	$117,430	$120,952	$124,581	$128,318	$132,168	$136,133
BMN-673 sales ($M)	**$81**	**$225**	**$234**	**$304**	**$316**	**$329**	**$342**	**$356**	**$370**	**$385**	**$401**	**$417**	**$434**	**$451**	**$469**
Probabilty Adjusted BMN-673 sales ($M)	**$48**	**$135**	**$140**	**$182**	**$190**	**$197**	**$205**	**$214**	**$222**	**$231**	**$240**	**$250**	**$260**	**$271**	**$282**
U.S. Olaparib Sales	**$48**	**$168**	**$175**	**$182**	**$190**	**$197**	**$205**	**$214**	**$222**	**$231**	**$240**	**$250**	**$260**	**$271**	**$282**
U.S. Niraparib Sales	**$48**	**$286**	**$362**	**$380**	**$400**	**$420**	**$442**	**$464**	**$222**	**$231**	**$240**	**$250**	**$260**	**$271**	**$282**
U.S. BMN-673 Sales	**$48**	**$135**	**$140**	**$182**	**$190**	**$197**	**$205**	**$214**	**$222**	**$231**	**$240**	**$250**	**$260**	**$271**	**$282**
Total U.S. Breast Cancer Sales	**$145**	**$589**	**$677**	**$745**	**$779**	**$815**	**$852**	**$891**	**$666**	**$693**	**$721**	**$750**	**$780**	**$812**	**$845**
Global Olaparib Sales	**$94**	**$262**	**$293**	**$301**	**$310**	**$319**	**$328**	**$337**	**$347**	**$357**	**$368**	**$379**	**$390**	**$402**	**$414**
Global Niraparib Sales	**$94**	**$379**	**$480**	**$499**	**$520**	**$541**	**$564**	**$588**	**$347**	**$357**	**$368**	**$379**	**$390**	**$402**	**$414**
Global BMN-673 Sales	**$94**	**$228**	**$258**	**$301**	**$310**	**$319**	**$328**	**$337**	**$347**	**$357**	**$368**	**$379**	**$390**	**$402**	**$414**
Total Global Breast Cancer Sales	**$256**	**$818**	**$1,090**	**$1,228**	**$1,277**	**$1,328**	**$1,382**	**$1,438**	**$666**	**$693**	**$721**	**$750**	**$780**	**$812**	**$845**

Source: Citi Research

Figure 40. European Market Model for PARP Inhibitors in Breast Cancer

	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E
Incidence Breast Cancer (Europe.)	309,580	312,675	315,802	318,960	322,150	325,371	328,625	331,911	335,230	338,583	341,969	345,388	348,842	352,331	355,854
% Local Disease	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*
Local Disease Patients	198,131	200,112	202,113	204,135	206,176	208,238	210,320	212,423	214,547	216,693	218,860	221,048	223,259	225,492	227,746
% Regional Disease	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*	*28%*
Regional Disease Patients	86,682	87,549	88,425	89,309	90,202	91,104	92,015	92,935	93,865	94,803	95,751	96,709	97,676	98,653	99,639
% Metastatic	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*
Metastatic Disease Patients	24,766	25,014	25,264	25,517	25,772	26,030	26,290	26,553	26,818	27,087	27,357	27,631	27,907	28,186	28,468
Surgical Candiates Patients	258,809	261,397	264,011	266,651	269,317	272,010	274,731	277,478	280,253	283,055	285,886	288,745	291,632	294,548	297,494
% Surgical Candidates that Relapse	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
Surgical Candidates that Relapse	51,762	52,279	52,802	53,330	53,863	54,402	54,946	55,496	56,051	56,611	57,177	57,749	58,326	58,910	59,499
Treatment Options															
Adjuvant Therapy Candidates	258,809	261,397	264,011	266,651	269,317	272,010	274,731	277,478	280,253	283,055	285,886	288,745	291,632	294,548	297,494
First Line Therapy Candidates	102,533	103,558	104,594	105,640	106,696	107,763	108,841	109,929	111,028	112,139	113,260	114,393	115,537	116,692	117,859
% Moving to 2nd-line therapy	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Second-Line Therapy Candidates	51,266	51,779	52,297	52,820	53,348	53,881	54,420	54,965	55,514	56,069	56,630	57,196	57,768	58,346	58,929
% BRCA Positve Eligible for PARP Inhibitors	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
PARP Inhibitor Treated BRCA Patients	10,253	10,356	10,459	10,564	10,670	10,776	10,884	10,993	11,103	11,214	11,326	11,439	11,554	11,669	11,786
% Olaparib Penetration	10%	20%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Patients treated with Olaparib	1,025	2,071	2,615	2,641	2,667	2,694	2,721	2,748	2,776	2,803	2,831	2,860	2,888	2,917	2,946
# Mos on therapy	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Price (month)	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500
Olaparib Price per patient per year (7 months PFS)	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000
Olaparib sales ($M)	**$77**	**$155**	**$196**	**$198**	**$200**	**$202**	**$204**	**$206**	**$208**	**$210**	**$212**	**$214**	**$217**	**$219**	**$221**
Probabilty Adjusted Olaparib sales ($M)	**$46**	**$93**	**$118**	**$119**	**$120**	**$121**	**$122**	**$124**	**$125**	**$126**	**$127**	**$129**	**$130**	**$131**	**$133**
% Niraparib Penetration	10%	20%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Patients treated with Niraparib	1,025	2,071	2,615	2,641	2,667	2,694	2,721	2,748	2,776	2,803	2,831	2,860	2,888	2,917	2,946
# Mos on therapy	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Price (month)	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500
Niraparib Price per patient per year	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000
Niraparib sales	**$77**	**$155**	**$196**	**$198**	**$200**	**$202**	**$204**	**$206**	**$208**	**$210**	**$212**	**$214**	**$217**	**$219**	**$221**
Probabilty Adjusted Niraparib sales ($M)	**$46**	**$93**	**$118**	**$119**	**$120**	**$121**	**$122**	**$124**	**$125**	**$126**	**$127**	**$129**	**$130**	**$131**	**$133**
% BMN-673 Penetration	10%	20%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Patients treated with BMN-673	1,025	2,071	2,615	2,641	2,667	2,694	2,721	2,748	2,776	2,803	2,831	2,860	2,888	2,917	2,946
# Mos on therapy	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Price (month)	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500	$12,500
Niraparib Price per patient per year	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000	$75,000
BMN-673 sales	**$77**	**$155**	**$196**	**$198**	**$200**	**$202**	**$204**	**$206**	**$208**	**$210**	**$212**	**$214**	**$217**	**$219**	**$221**
Probabilty Adjusted BMN-673 sales ($M)	**$46**	**$93**	**$118**	**$119**	**$120**	**$121**	**$122**	**$124**	**$125**	**$126**	**$127**	**$129**	**$130**	**$131**	**$133**
Europe Olaparib Sales	**$46**	**$93**	**$118**	**$119**	**$120**	**$121**	**$122**	**$124**	**$125**	**$126**	**$127**	**$129**	**$130**	**$131**	**$133**
Europe Niraparib Sales	**$46**	**$93**	**$118**	**$119**	**$120**	**$121**	**$122**	**$124**	**$125**	**$126**	**$127**	**$129**	**$130**	**$131**	**$133**
Europe BMN-673 Sales	**$46**	**$93**	**$118**	**$119**	**$120**	**$121**	**$122**	**$124**	**$125**	**$126**	**$127**	**$129**	**$130**	**$131**	**$133**
Total Europe Breast Cancer Sales	**$138**	**$280**	**$353**	**$357**	**$360**	**$364**	**$367**	**$371**	**$375**	**$378**	**$382**	**$386**	**$390**	**$394**	**$398**

Source: Citi Research

Olaparib in Gastric Cancer Is Promising

Olaparib + Paclitaxel Data At ASCO Is Encouraging

At ASCO, AstraZeneca will also show positive ph 2 data testing olaparib + paclitaxel vs. paclitaxel alone in 124 2nd-line gastric cancer patients. In the study, 50% of pts had low ATM tumors (ATM–) vs. 14% in the general population. The reason this population was selected is because cell culture data has shown that gastric cancer cells that have low ATM protein levels are sensitive to olaparib.

Olaparib + paclitaxel showed a statistically significant improvement in OS (13.1 vs. 8.3 mos), but not PFS (3.9 vs 3.6 mos) vs. paclitaxel alone in both all pts and ATM– pts. But there was a larger benefit in ATM– pts (OS: not reached vs. 8.2 mos).

This data provides proof of concept and will likely drive AstraZeneca to initiate ph 3 studies. As expected, the key toxicity of the combo was low blood cell counts.

Figure 41. Olaparib in Combination with Paclitaxel in Gastric Cancer

All Patients	Olaparib + Paclitaxel	Paclitaxel	HR (p value)
n	62	62	
PFS (Mos)	3.9	3.6	HR=0.80 (p=0.261)
OS (Mos)	13.1	8.3	HR=0.56 (p=0.010)
Evaluable for Response			
n	53	47	
ORR %	26.4	19.1	HR=1.65 (P=0.323)
ATM– Patients			
n	31	32	
PFS (Mos)	5.3	3.7	HR=0.74 (P=0.315)
OS (Mos)	NC	8.2	HR=0.35 (P=0.003)
Evaluable for Response			
n	26	23	
ORR %	34.6	26.1	OR=1.76 (P=0.390)

Source: ASCO 2013

Figure 41. BMN-673 Activity in SCLC Lines

Cell name	BMN673 IC50
NCI-H446	13
NCI-H1930	4.1
NCI-H69	5.15
NCI-H524	3.1
NCI-H1092	8.55
NCI-H2107	7.3
COR-L279	15
NCI-H2081	6.3
NCI-H209	1.7
NCI-H1048	2.2
NCI-H1092	9.25
DMS-79	9.25

Source: BioMarin

PARP Inhibitors in Other Cancers

Preclinical Data Indicates PARP Inhibition Might Work in Small Cell Lung Cancer

Proteomic profiling has shown that PARP1 is two fold over expressed in small cell lung cancer (SCLC) cell lines vs non-small cell lung cancer (NSCLC). In addition, there are other DNA repair proteins that are also over expressed in SCLC cell lines.

Data has also shown that SCLC had comparable or better sensitivity to PARP inhibitors compared to breast cancer cell lines. In these experiments, markers for response to BMN-673 overlapped with markers of cisplatin sensitivity. This data confirms other results showing that PARP inhibitors have higher activity in platinum sensitive cancers.

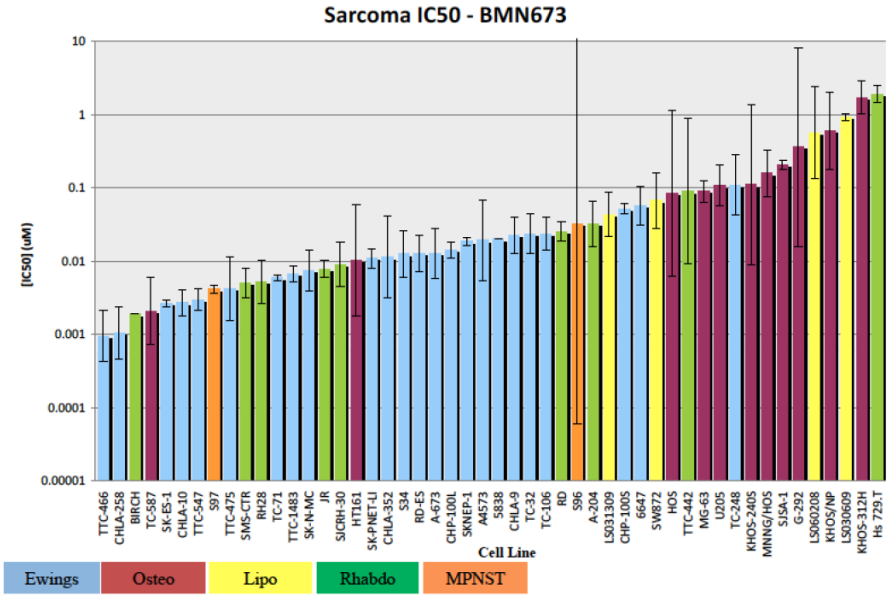
These preliminary preclinical data show that PARP inhibitors may find use in treatment of small cell lung cancer. Further clinical trials are needed to confirm how these preclinical data pans out in clinical trials.

Biomarin will investigate the activity of BMN-673 and the response biomarkers in its ph 1 cohort expansion study.

Preclinical Data Indicates PARP Inhibition Might Have Role in Ewing's Sarcoma

Ewing's sarcoma is a malignant neoplasm of bone and soft tissue, which is very difficult to treat. Preclinical data show that sarcoma cell lines are sensitive to BioMarin's BMN-673. These preclinical findings suggest that targeted therapy with PARP inhibitors in Ewing's sarcoma should be explored in clinical setting.

Figure 42. BMN-673 Effectively Inhibits Sarcoma Cell Lines



Source: BioMarin

AstraZeneca PLC

Valuation (AZN.L; £34.39; 2)

Our £35 target price reflects a target multiple of c.11x 2014E core earnings, a c.20% discount to the EU large-cap pharma multiple (inc Novo) of 13.5x, reflecting AZN's weak anticipated core EPS growth, coupled with a higher risk premium due to the lack of diversification compared with peers, and uncertainty as to what the new CEO will do to change the strategic direction of the company.

Our forecasts anticipate that AZN will grow core EPS at -4% over the 2014-19E time frame, compared with 8% for the EU peer group.

Our DCF-derived Intrinsic Value is £36.5. We project free cash flows for an explicit 10-year period and thereafter apply terminal growth assumptions. Consistent with our sector methodology, which makes use of the CAPM to calculate the cost of equity, we use a WACC of 8.5% and assume a 0% terminal growth rate. In the absence of evidence for new internal or external drivers of value, we acknowledge the company's secure high free cash flow and dividend yields.

Risks

Downside risks include anticipated generic timings, slowing sales growth in emerging markets, and pressure to Symbicort market share gains in the US.

Upside risks include higher-than-anticipated uptake of Brilinta or diabetes assets (Onglyza, Bydureon, Forxiga) and an acceleration in value-enhancing licensing activities or M&A, thereby increasing the long-term growth profile of the company.

BioMarin Pharmaceutical

Valuation (BMRN.O; US$63.85; 1)

Our 12-month target price of $79 is based on a sum-of-the-parts analysis of the net present value of the major product lines and net cash position. We include all the current marketed products as well as GALNS (90% probability of approval), BMN-701 (75% probability of approval), BMN-673 (60% probability of approval) and PEG-PAL (70% probability of approval). A SOTP analysis provides the best measure of the value of the underlying assets of the company and accounts for their respective operating margins.

We do not include any sales for rest of the pipeline in our SOTP analysis at the present time, which represent upside to our current valuation

Our sum of parts valuation includes Nagalyzyme ($16.1), Aldurazyme ($9.6), Kuvan ($2.9), Firdapse ($0.7), GALNS ($23.2), BMN-701($10.0) (BMN-673 ($5.0) and PEG-PAL ($8.9) as well as $2.6 in net cash. We assume that Kuvan and Firdapse will face generic erosion as those drugs are small molecules.

Risks

Key risks facing the business include: (1) clinical and regulatory approval risks for GALNS, PEG-PAL, BMN-673 and BMN-701, (2) generic risks for Kuvan and Firdapse (both are small molecules) and we expect paragraph IV filing for Kuvan at any time, and (3) reimbursement risks as Aldurazyme, Naglazyme, and Kuvan are high priced therapies that are sold extensively to many countries around the globe.

If the impact from the above risks turns out to be greater than expected, the shares could fail to achieve our target price.

Tesaro

Valuation (TSRO.O; US$33.10; 1H)

Our 12-month target price of $43 is derived using a 25x P/E multiple on Tesaro's 2018 non GAAP, fully-taxed EPS estimate of $3.32, discounted back at 20%. Our 2018 EPS is the company's first year of profitability.

Using the average P/E multiple that emerging biotechnology companies typically trade at during their first year of profitability is the most direct and appropriate method, in our view. This is because it represents what investors are willing to pay for biopharmaceutical companies that just joined the ranks of profitable companies with solid growth prospects ahead.

We use a 25x multiple since it accurately reflects the promise of rolapitant for CINV and niraparib for ovarian and breast cancers. We typically attribute 20x-35x multiples on launch products and we can argue that a 25x multiple is fairly conservative given our expectations for a strong launch of rolapitant and niraparib and Tesaro's operating leverage.

Due to clinical, regulatory and commercial uncertainties, we incorporate a 20% discount rate to Tesaro's EPS (when discounting back from 2018 to 2013 to apply a forward multiple). This is significantly higher than the company's cost of capital, but reflects the additional risks inherent in companies in clinical stage development with only phase 2 data.

We also conducted a discounted cash flow analysis of Tesaro to obtain a second valuation. We note that this analysis is only supportive and our target price is based on the P/E valuation methodology only.

In our DCF analysis, we extend our estimates until 2033. We assume no terminal value. According to our analysis, Tesaro's DCF value is $42.

Risks

We attribute a High Risk rating to the stock since Tesaro is facing several clinical, regulatory, commercial, and financial risks.
Rolapitant is currently enrolling patients in three phase 3 studies. Oral rolapitant has shown similar efficacy to Emend in HEC regimens but has not yet been tested in MEC. The drug is also facing typical ph 3 clinical risks.
Given that the oral formulation of Emend will go generic in 2015 and IV in 2019, rolapitant may not be able to garner much commercial success when facing cheap generic competition unless it shows distinct clinical differentiation. As a result, sales may disappoint.
Tesaro also does not have any commercial capabilities and will need to hire an experienced sales force to build the needed infrastructure.
Niraparib is also facing typical clinical risks of a ph 3 asset while TSR-011 is in early clinical development and as a long path ahead towards approval in the competitive ALK class of drugs.
Tesaro also needs to raise further capital before achieving profitability.
If the impact of these risk factors is greater than we anticipate, shares may have difficulty achieving our target price.

Appendix A-1

Analyst Certification

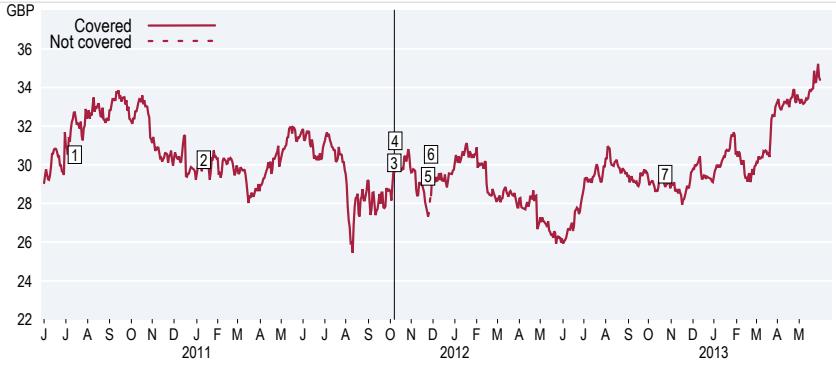
The research analyst(s) primarily responsible for the preparation and content of this research report are named in bold text in the author block at the front of the product except for those sections where an analyst's name appears in bold alongside content which is attributable to that analyst. Each of these analyst(s) certify, with respect to the section(s) of the report for which they are responsible, that the views expressed therein accurately reflect their personal views about each issuer and security referenced and were prepared in an independent manner, including with respect to Citigroup Global Markets Inc and its affiliates. No part of the research analyst's compensation was, is, or will be, directly or indirectly, related to the specific recommendation(s) or view(s) expressed by that research analyst in this report.

IMPORTANT DISCLOSURES

AstraZeneca PLC (AZN.L)

Ratings and Target Price History
Fundamental Research

Analyst: Mark Dainty, ACA
Covered since October 24 2012



	Date	Rating	Target Price	Closing Price
1	14-Jul-10	2M	*33.00	32.71
2	12-Jan-11	*1M	*34.00	30.14
3	7-Oct-11	Stock rating system changed		
4	8-Oct-11	*1	34.00	29.61
5	24-Nov-11	Coverage terminated		
6	29-Nov-11	*2	*28.00	28.41
7	24-Oct-12	2	*30.00	28.85

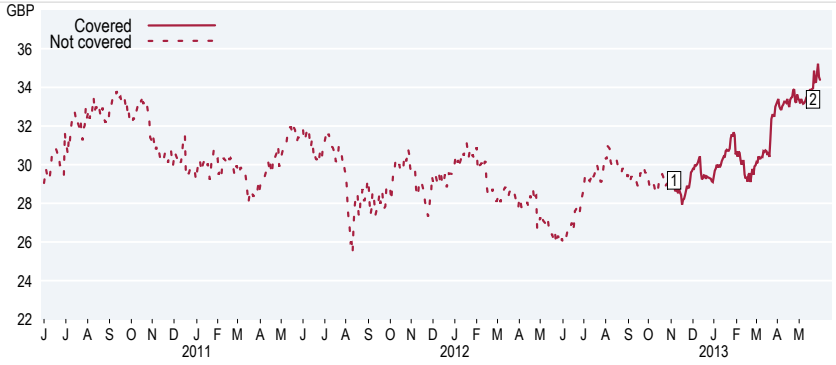
* Indicates change

Rating/target price changes above reflect Eastern Standard Time

AstraZeneca PLC (AZN.L)

Ratings and Target Price History
Best Ideas Research
Relative Call (3 Month)

Analyst: Mark Dainty, ACA
Covered since October 24 2012



	Date	Rating	Target Price	Closing Price
1	6-Nov-12	*ADD LP	-	29.10
2	21-May-13	*REM LP	-	33.95

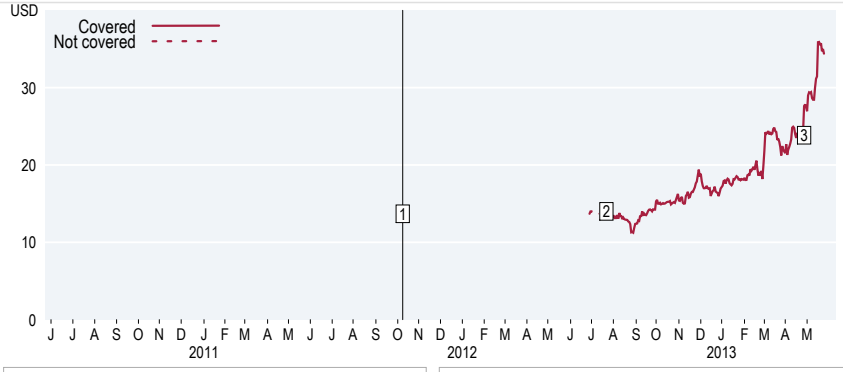
* Indicates change

Rating/target price changes above reflect Eastern Standard Time

Tesaro (TSRO)

Ratings and Target Price History
Fundamental Research

Analyst: Yaron Werber, MD
Covered since July 23 2012



	Date	Rating	Target Price	Closing Price
1	8-Oct-11	Stock rating system changed		
2	23-Jul-12	*1H	*21.00	13.90
3	26-Apr-13	1H	*31.00	27.62

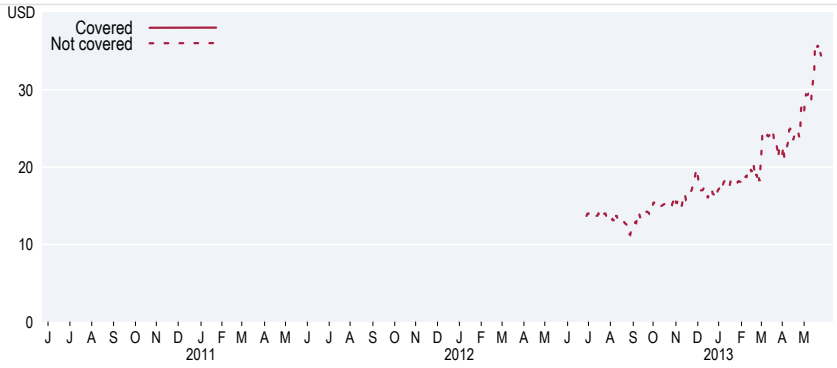
* Indicates change

Rating/target price changes above reflect Eastern Standard Time

Tesaro (TSRO)

Ratings and Target Price History
Best Ideas Research
Relative Call (3 Month)

Analyst: Yaron Werber, MD
Covered since July 23 2012



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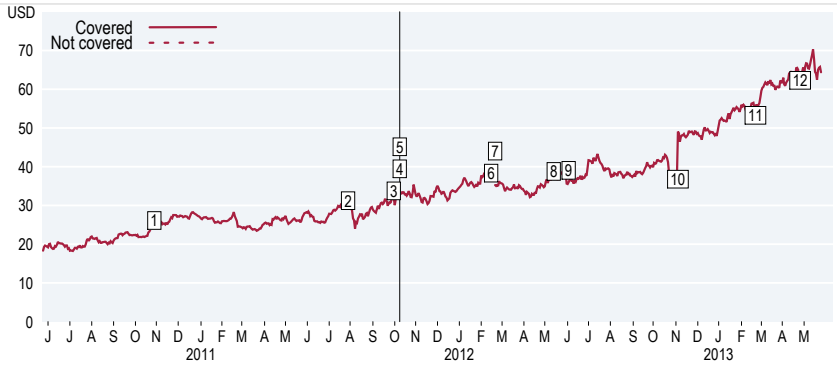
Rating/target price changes above reflect Eastern Standard Time

BioMarin Pharmaceutical (BMRN)

Ratings and Target Price History
Fundamental Research

Analyst: Yaron Werber, MD
Covered since February 21 2012



	Date	Rating	Target Price	Closing Price
1	28-Oct-10	1H	*31.00	24.62
2	28-Jul-11	1H	*35.00	29.29
3	30-Sep-11	1H	*39.00	31.87
4	8-Oct-11	Stock rating system changed		

	Date	Rating	Target Price	Closing Price
5	8-Oct-11	*1	39.00	33.34
6	15-Feb-12	Coverage terminated		
7	21-Feb-12	1	*45.00	35.26
8	12-May-12	1	*49.00	38.00

	Date	Rating	Target Price	Closing Price
9	4-Jun-12	1	*47.00	36.00
10	5-Nov-12	1	*61.00	49.07
11	21-Feb-13	1	*67.00	53.27
12	25-Apr-13	1	*72.00	62.87

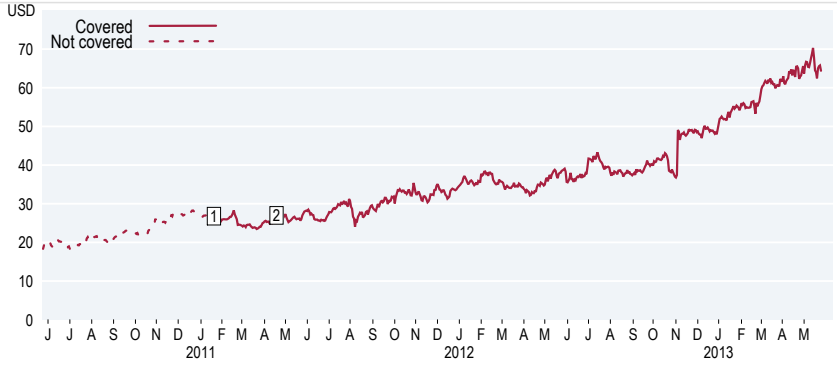
* Indicates change

Rating/target price changes above reflect Eastern Standard Time

BioMarin Pharmaceutical (BMRN)

Ratings and Target Price History
Best Ideas Research
Relative Call (3 Month)

Analyst: Yaron Werber, MD
Covered since February 21 2012



	Date	Rating	Target Price	Closing Price
1	20-Jan-11	*ADD MP	-	25.94

	Date	Rating	Target Price	Closing Price
2	19-Apr-11	*REM MP	-	26.45

* Indicates change

Rating/target price changes above reflect Eastern Standard Time

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Data current as of 31 Mar 2013	**Buy**	**Hold**	**Sell**	**Buy**	**Hold**	**Sell**
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