

Initiation report

PRR's C-Vac is a potentially elegant therapy for recurrent ovarian cancer

November 1, 2011

Rating Starts at	Buy
Target price Starts at	AUD 0.31
Closing price October 31, 2011	AUD 0.19
Potential upside	+63.2%

Action: PRR is developing an ovarian cancer recurrence vaccine called C-Vac

PRR hopes to commercialise an ovarian cancer recurrence immunotherapeutic vaccine. As a part of the C-Vac process, PRR sensitises the patient's own dendritic immune cells against components of the patient's ovarian cancer. These sensitised dendritic cells then attach to ovarian cancer cells, and transport them to the immune system complexes, where the cancer cells are destroyed. We believe that immunotherapy is an interesting technology in that it uses the body's own processes to destroy cancer cells, thus decreasing the side-effect profile of the treatment compared to external chemotherapeutic agents.

Catalyst: PRR will begin a Phase III clinical trial by 4QCY11 in C-Vac

Final data from this Phase III clinical trial is likely to be released in CY14. Up until that time, we will be watching for the release of Phase IIb clinical trial data (4QCY12) and potential partnering opportunities.

Valuation: Initiating with a Buy recommendation, TP AUD0.31

We have estimated the recurrence of the ovarian cancer market. We believe the potential market size for PRR's C-Vac treatment is in the order of cUSD2bn per annum. Assuming that PRR treats 25% of those females with recurrence of epithelial ovarian cancer, then its potential market is cUSD500mn pa. Our risk-weighted valuation and price target for PRR is AUD0.31 per share. At present, there have been no significant adverse effects or health issues, and PRR's Phase II trials indicate a product with the potential for market viability. Therefore, we believe this is an investment opportunity for investors with a higher risk appetite.

30 Jun	FY11	FY12F		FY13F		FY14F	
Currency (AUD)	Actual	Old	New	Old	New	Old	New
Revenue (mn)	0		1		1		1
Reported net profit (mn)	-21		-15		-14		-15
Normalised net profit (mn)	-21		-15		-14		-15
Normalised EPS	-2.51c		-1.58c		-1.29c		-1.17c
Norm. EPS growth (%)	na		na		na		na
Norm. P/E (x)	na	N/A	na	N/A	na	N/A	na
EV/EBITDA (x)	na		na		na		na
Price/book (x)	3.4	N/A	4.7	N/A	3.1	N/A	3.9
Dividend yield (%)	na	N/A	na	N/A	na	N/A	na
ROE (%)	-59.4		-32.7		-24.9		-21.3
Net debt/equity (%)	net cash		net cash		net cash		net cash

Source: Nomura estimates

Key company data: See page 2 for company data and detailed price/index chart.

Anchor themes

PRR hopes to commercialise an ovarian cancer recurrence immunotherapeutic vaccine. We believe that immunotherapy is an interesting technology in that it uses the body's own processes to destroy cancer cells, thus decreasing the side-effect profile of the treatment compared to external chemotherapeutic agents.

Nomura vs consensus

There is minimal consensus data available.

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See Appendix A-1 for analyst certification, important disclosures and the status of non-US analysts.

Key data on Prima Biomed Ltd

Income statement (AUDmn)

Year-end 30 Jun	FY10	FY11	FY12F	FY13F	FY14F
Revenue	0	0	1	1	1
Cost of goods sold	0	0	0	0	0
Gross profit	0	0	1	1	1
SG&A	-12	-16	-18	-17	-18
Employee share expense	0	0	0	0	0
Operating profit	-12	-16	-17	-17	-17
EBITDA	-11	-16	-17	-17	-17
Depreciation	0	0	0	0	0
Amortisation	0	0	0	0	0
EBIT	-12	-16	-17	-17	-17
Net interest expense	-6	-5	2	2	3
Associates & JCEs	0	0	0	0	0
Other income	0	0	0	0	0
Earnings before tax	-18	-21	-15	-14	-15
Income tax	0	0	0	0	0
Net profit after tax	-18	-21	-15	-14	-15
Minority interests	0	0	0	0	0
Other items	0	0	0	0	0
Preferred dividends	0	0	0	0	0
Normalised NPAT	-18	-21	-15	-14	-15
Extraordinary items	0	0	0	0	0
Reported NPAT	-18	-21	-15	-14	-15
Dividends	0	0	0	0	0
Transfer to reserves	-18	-21	-15	-14	-15

Valuation and ratio analysis

FD normalised P/E (x)	na	na	na	na	na
FD normalised P/E at price target (x)	na	na	na	na	na
Reported P/E (x)	na	na	na	na	na
Dividend yield (%)	na	na	na	na	na
Price/cashflow (x)	na	na	na	na	na
Price/book (x)	8.4	3.4	4.7	3.1	3.9
EV/EBITDA (x)	na	na	na	na	na
EV/EBIT (x)	na	na	na	na	na
Gross margin (%)	na	na	71.9	72.0	71.7
EBITDA margin (%)	na	na	-2,123.7	-1,986.8	-2,041.5
EBIT margin (%)	na	na	-2,131.6	-1,994.5	-2,049.1
Net margin (%)	na	na	-1,906.8	-1,715.3	-1,711.5
Effective tax rate (%)	na	na	na	na	na
Dividend payout (%)	na	na	na	na	na
Capex to sales (%)	na	na	2.8	2.7	2.6
Capex to depreciation (x)	8.6	2.0	1.0	1.0	1.0
ROE (%)	na	-59.4	-32.7	-24.9	-21.3
ROA (pretax %)	-165.3	-130.5	-147.6	-141.8	-147.7

Growth (%)

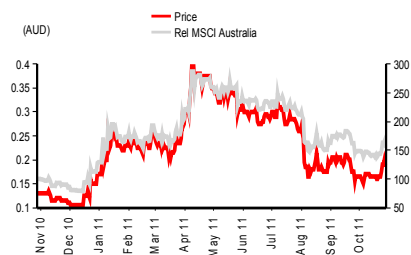
Revenue	na	na	na	2.8	1.6
EBITDA	na	na	na	na	na
EBIT	na	na	na	na	na
Normalised EPS	na	na	na	na	na
Normalised FDEPS	na	na	na	na	na

Per share

Reported EPS (AUD)	-3.21c	-2.51c	-1.58c	-1.29c	-1.17c
Norm EPS (AUD)	-3.21c	-2.51c	-1.58c	-1.29c	-1.17c
Fully diluted norm EPS (AUD)	-2.50c	-2.15c	-1.40c	-1.15c	-1.06c
Book value per share (AUD)	0.02	0.06	0.04	0.06	0.05
DPS (AUD)	0.00	0.00	0.00	0.00	0.00

Source: Nomura estimates

Relative performance chart (one year)



Source: ThomsonReuters, Nomura research

(%)	1M	3M	12M
Absolute (AUD)	15.2	-28.3	46.2
Absolute (USD)	24.0	-30.7	59.6
Relative to index	7.3	-26.0	53.8
Market cap (USDmn)	225.0		
Estimated free float (%)	100.0		
52-week range (AUD)	.42/.1		
3-mth avg daily turnover (USDmn)	2.53		
Major shareholders (%)			
Laurence Freedman	3.5		
Martin Rogers	2.6		

Source: Thomson Reuters, Nomura research

Notes

We expect PRR to have a cash burn rate of AUD1.5mn per month

Cashflow (AUDmn)

Year-end 30 Jun	FY10	FY11	FY12F	FY13F	FY14F
EBITDA	-11	-16	-17	-17	-17
Change in working capital	-9	1	0	1	1
Other operating cashflow	14	5	2	2	3
Cashflow from operations	-6	-10	-15	-14	-14
Capital expenditure	0	0	0	0	0
Free cashflow	-7	-10	-15	-14	-14
Reduction in investments	0	0	0	0	0
Net acquisitions	0	0	0	0	0
Reduction in other LT assets	0	0	0	0	0
Addition in other LT liabilities	0	0	0	0	0
Adjustments	-10	0	0	0	0
Cashflow after investing acts	-17	-10	-15	-14	-14
Cash dividends	0	0	0	0	0
Equity issue	15	45	0	50	0
Debt issue	6	5	0	0	0
Convertible debt issue	0	0	0	0	0
Others	0	0	0	0	0
Cashflow from financial acts	21	50	0	50	0
Net cashflow	5	40	-15	36	-14
Beginning cash	1	6	46	31	67
Ending cash	6	46	31	67	53
Ending net debt	-5	-46	-31	-67	-53

Source: Nomura estimates

Notes

We forecast PRR will require a AUD50mn equity raising in FY13F

Balance sheet (AUDmn)

As at 30 Jun	FY10	FY11	FY12F	FY13F	FY14F
Cash & equivalents	6	46	31	67	53
Marketable securities	0	0	0	0	0
Accounts receivable	0	0	0	0	0
Inventories	0	0	0	0	0
Other current assets	11	11	11	11	11
Total current assets	17	57	42	78	65
LT investments	1	0	0	0	0
Fixed assets	0	0	0	0	0
Goodwill	0	0	0	0	0
Other intangible assets	0	0	0	0	0
Other LT assets	0	0	0	0	0
Total assets	18	58	43	79	65
Short-term debt	1	0	0	0	0
Accounts payable	1	2	3	4	4
Other current liabilities	0	0	0	0	0
Total current liabilities	2	3	3	4	4
Long-term debt	0	0	0	0	0
Convertible debt	0	0	0	0	0
Other LT liabilities	0	0	0	0	0
Total liabilities	2	3	3	4	4
Minority interest	0	0	0	0	0
Preferred stock	0	0	0	0	0
Common stock	75	135	135	185	185
Retained earnings	-59	-80	-95	-110	-124
Proposed dividends	0	0	0	0	0
Other equity and reserves	0	0	0	0	0
Total shareholders' equity	16	55	40	75	61
Total equity & liabilities	18	58	43	79	65

Notes

PRR had cash and cash investments totalling AUD56mn as at 30 June 2011

Liquidity (x)

Current ratio	7.50	22.49	13.90	21.64	14.92
Interest cover	-1.8	-3.0	na	na	na

Leverage

Net debt/EBITDA (x)	na	na	na	na	na
Net debt/equity (%)	net cash	net cash	net cash	net cash	net cash

Activity (days)

Days receivable	na	na	17.8	20.7	24.5
Days inventory	na	na	378.9	441.8	516.6
Days payable	na	na	4,368.2	5,093.7	5,956.1
Cash cycle	na	na	-3,971.5	-4,631.2	-5,415.0

Source: Nomura estimates

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Executive Summary

Prima Biomed (PRR) is a specialty pharmaceutical company. The group's major focus is producing human healthcare products to treat and manage ovarian cancer.

PRR is developing treatments against ovarian cancer, based on the development of an immunotherapeutic vaccine

PRR is developing treatments against ovarian cancer, based on the development of an ovarian cancer recurrence immunotherapeutic vaccine. Immunotherapy is a medical term defined as the "treatment of disease by inducing, enhancing or suppressing an immune response". Immunotherapies that activate the immune response are classified as activation immunotherapies. PRR's C-Vac product is an activation immunotherapy that uses dendritic cell-based immunotherapy against ovarian cancer. For the purposes of this report, we will focus on PRR's technology platform known as C-Vac.

We believe PRR's label claim will be for treatment of epithelial ovarian cancer post-remission from first-line chemotherapy. The tumour will have to be positive on immunohistochemistry to Mucin-1.

Catalysts that will move the stock

We believe there are a number of potential near-term catalysts for the stock, including the successful conclusion of clinical trials. Should these turn out to be positive, this would imply a further confirmation of PRR's technology and business model. Hence, we would expect the share price to react positively.

Sector/strategic context

PRR hopes to develop treatments for recurrent ovarian cancer. Given the lack of options at present for these patients, this is an attractive market segment, in our view.

Valuation methodology

According to data from Tufts University, USA, the probability of success of clinical trials depends upon the stage of the clinical trial. This is seen in the following figure. We ascribe a 62.4% risk-weighting for the C-Vac opportunity, as we believe PRR will begin a Phase III clinical trial by 4QCY11.

Fig. 1: Probability of drug at clinical trial stage ultimately getting to market (Tufts DiMasi data)

Phase	Probability of success of moving to next phase (%)	Probability of drug getting on market from particular phase (%)
Phase I	62.5	13.4
Phase II	35	21.4
Phase III	68	61.2
Filing	90	90.0

Source: PubMed, Nomura research

Our valuation is seen in the following figure.

Fig. 2: PRR – valuation methodology

Valuation of PRR R&D portfolio (A\$)	
CVac	\$0.50
Probability (%)	61.2
Risk weighted valuation	\$0.31

Source: Nomura estimates, company data

Risks to our investment view

There is still a good deal of uncertainty around PRR's viability in most of its prospective markets. Early clinical trials, although positive, give no real enough indication of a product's true viability and full foresight on future market conditions is difficult to obtain. In its favour, PRR's base product is found naturally in the body, and we see little reason to believe that injections of sensitized cells back into the body would cause serious health issues or be relatively less effective in doing their natural job. To date, all preclinical and Phase II trials have shown indications for product viability. As it stands, there have been no significant adverse effects or health issues and Phase II trials indicate a product with the potential for market viability. Therefore, we believe this is an investment opportunity for investors with a higher risk appetite.

Our investment case for PRR

Bull points

- **Elegant technology:** We believe that immunotherapy is an interesting technology in that it uses the body's own processes to destroy cancer cells, thus decreasing the side-effect profile of the treatment compared to external chemotherapeutic agents;
- **Large opportunity:** We believe the opportunity is large and likely to be reimbursed well. The World Health Organisation (WHO) predicts that c70,000 females (aged 0-75 years) in the US and EU will be diagnosed with ovarian cancer in 2011. Of which, c85% will have epithelial-type ovarian cancer which is targeted by PRR's treatment. We believe approximately 65% or 39,000 patients will be eligible for surgery because their cancer is likely to be diagnosed as stage I-III, based on historical distribution patterns. Of these, we note that 70% of optimally debulked ovarian cancer patients are likely to have recurrence 24 months later, on the basis of historical recurrence patterns. Of these, we assume that 80% of recurrent ovarian cancer patients have the MUC-1 type, which would be sensitive to PRR's C-Vac treatment. If we assume that each treatment would be reimbursed at USD90,000 per annum (in line with reimbursement rates from US public and private insurers for Dendreon's Provenge, which treats prostate cancer), then the potential market size for PRR's C-Vac treatment is in the order of cUSD2bn per annum. Assuming that PRR treats 25% of those females with recurrence of epithelial ovarian cancer, then we forecast its potential market size is cUSD500mn pa;
- **Orphan drug designation:** Whilst patent life for C-Vac lasts only to 2018, C-Vac does have marketing exclusivity for up to 10 years post marketing approval;
- **Management:** We believe the clinical team is of a high standard. We believe this increases the possibility of a properly designed trial process and this should support registration of the product;
- **Middle East revenue:** PRR is seeking early revenues via its Middle Eastern opportunity. In May 2011, PRR announced that Dubai Healthcare City (DHCC) has granted approval for the marketing and distribution of C-Vac in DHCC;
- **Strong cash balance:** PRR's cash balance was AUD56mn as at 30 June 2011. PRR is targeting expenditure of AUD1.4-1.7mn per month during the course of its phase III clinical trial; and
- **Path to market:** PRR has a path to market – it can follow Dendreon (DNDN US, not rated) which is in the US market with Provenge, an immunotherapy prostate cancer recurrence vaccine. As a fast follower, we believe PRR's manufacturing technology has the potential to be better than DNDN's.

Fig. 3: PRR – outline of clinical trials and stages

Trial stage	Preclinical	Phase I trial	Phase II trial	Phase III trial
General time until cashflow	7 years+	5-7 years	3-5 years	1-2 years
General probability of product getting to market	c10%	13%	21%	61%
Cost of trials	cUS\$5m	cUS\$5-10m	cUS\$20m	cUS\$50-100m
PRR products - indications and stages of development				
C-Vac				
Oral HPV Vaccine				
Anti-Cripto-1 Mab				

Source: Nomura estimates

Bear points

These include:

- **C-Vac has to get through Phase III trials:** There is no guarantee that Phase II trials will lead to positive Phase III trials. We note that the Phase II trial has not demonstrated statistically significant results so far. Hence, the Phase III clinical trial will assess statistical significance of the response to C-Vac;

- **Further capital raising may be required:** We believe it is likely that PRR will have to come back to the market to continue its Phase III clinical trials. After a successful capital raising, PRR had AUD56mn in cash as at 30 June 2011. It plans an 800-patient clinical trial. We believe the cost of performing a Phase III clinical trial can be up to USD60K per patient or more. If this is the case, then it would cost USD48mn for the clinical trial. This does not include other costs including infrastructure;
- **Timelines:** Our analysis of the timelines for potential release of data from the Phase III clinical trial is that the final data is unlikely to be released until CY14;
- **No partner at this stage:** We believe a US-based partner would give validation to the PRR processes and would likely help in getting the product to market; and
- **Cashflows:** Should the trial be successful, we note that the company is unlikely to receive EU or US revenues for its product until FY16F.

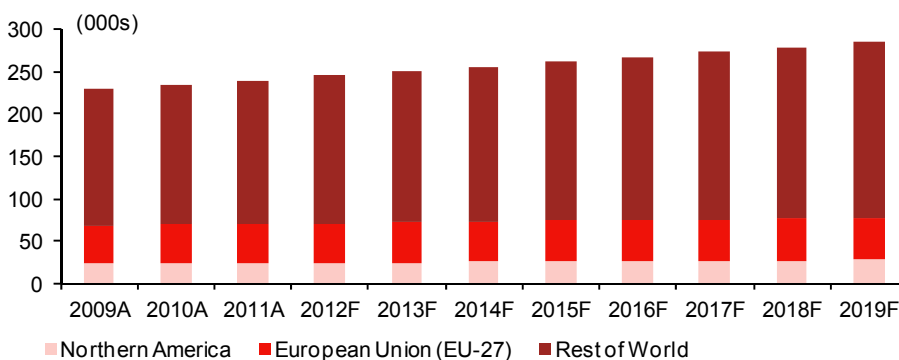
Background – What is ovarian cancer?

Definition and incidence of ovarian cancer

Ovarian cancer is a cancer that forms in tissues of the ovary (one of a pair of female reproductive glands in which the ova, or eggs, are formed). Most ovarian cancers are either ovarian epithelial carcinomas (cancer that begins in the cells on the surface of the ovary) or malignant germ cell tumours (cancer that begins in egg cells).

In the US, ovarian cancer afflicts approximately 22,000 women with a lifetime risk of one in 70, making it the fifth most lethal cancer, accounting for 15,000 deaths in 2009. The most common histologies are serous, endometrioid and mucinous, with rare transitional and clear cell variants. Although treatable, ovarian cancer is seldom curable. More than 70% of women present with stage III or IV disease due to rapid progression and the insidious onset of symptoms, and lack of effective screening tests. Therapy for ovarian cancer has evolved over the past 30 years to include upfront maximal surgical cytoreduction by a gynaecologic oncologist surgeon followed by chemotherapy. Multiple large Phase III trials have demonstrated that approximately 75% of women will respond to this upfront treatment, with a median clinical remission time of 16-18 months.

Fig. 4: Incidence of ovarian cancer in women aged 0-75yrs



Source: Globocan

To diagnose ovarian cancer, the following tests are usually performed:

- **Physical exam:** Abdominal exam to check for tumours or an abnormal build-up of fluid (ascites). A sample of fluid can be taken to look for ovarian cancer cells.
- **Pelvic exam:** The ovaries and nearby organs are examined for lumps or other changes in their shape or size. A Pap test is part of a normal pelvic exam, but it is not used to collect ovarian cells. The Pap test detects cervical cancer. The Pap test is not used to diagnose ovarian cancer.
- **Blood tests:** The lab may check the level of several substances, including CA-125. CA-125 is a substance found on the surface of ovarian cancer cells and on some normal tissues. A high CA-125 level could be a sign of cancer or other conditions. The CA-125 test is not used alone to diagnose ovarian cancer. This test is approved by the Food and Drug Administration for monitoring a woman's response to ovarian cancer treatment and for detecting its return after treatment.
- **Ultrasound:** The device aims sound waves at organs inside the pelvis. The waves bounce off the organs. A computer creates a picture from the echoes. The picture may show an ovarian tumour.
- **Biopsy:** A biopsy is the removal of tissue or fluid to look for cancer cells. Based on the results of the blood tests and ultrasound, surgery may be an option (a laparotomy) to remove tissue and fluid from the pelvis and abdomen. Surgery is usually needed to diagnose ovarian cancer.

These are four stages of ovarian cancer:

- **Stage I:** Cancer cells are found in one or both ovaries. Cancer cells may be found on the surface of the ovaries or in fluid collected from the abdomen.
- **Stage II:** Cancer cells have spread from one or both ovaries to other tissues in the pelvis. Cancer cells are found on the fallopian tubes, the uterus, or other tissues in the pelvis. Cancer cells may be found in fluid collected from the abdomen.
- **Stage III:** Cancer cells have spread to tissues outside the pelvis or to the regional lymph nodes. Cancer cells may be found on the outside of the liver.
- **Stage IV:** Cancer cells have spread to tissues outside the abdomen and pelvis. Cancer cells may be found inside the liver, in the lungs, or in other organs.

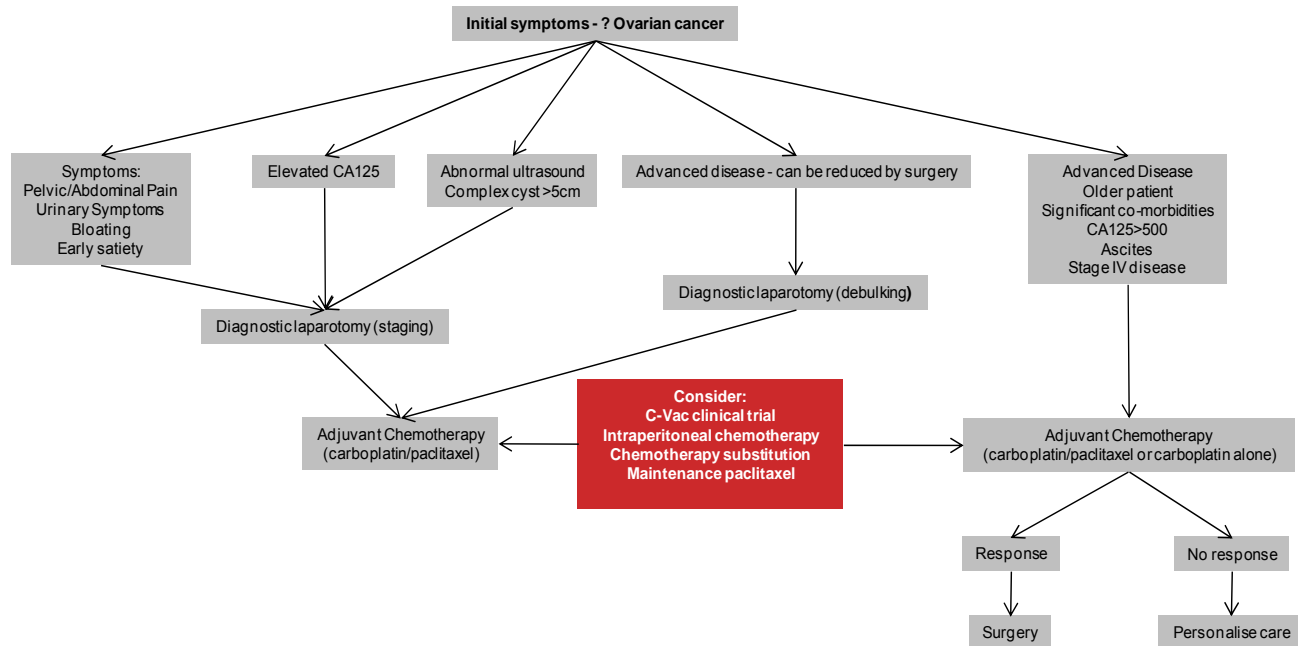
We believe the PRR vaccine will initially be aimed at later-stage ovarian cancer, and specifically at ovarian cancer recurrence.

Current management of ovarian cancer

The management of ovarian cancer encompasses a combination of surgical resection and chemotherapy. Over the last several decades, clinical trial results have led to an evolution in the management of ovarian cancer. In 2006, for the first time, a median overall survival (OS) of greater than five years was reported among advanced stage ovarian cancer patients treated in a randomized controlled trial setting. We enclose an initial treatment algorithm for ovarian cancer in the following figure.

The five-year relative survival rate for Australian women with ovarian cancer has increased significantly, from 33% in 1982-1987 to 40% in 2000-2006

Fig. 5: Ovarian cancer – initial treatment algorithm



Source: PubMed

Recurrence rates high for ovarian cancer

While increasing numbers of patients with ovarian cancer are experiencing five-year survival, 90% of sub-optimally debulked patients and 70% of optimally debulked patients relapse 18 to 24 months following primary treatment. Hence, there is a great deal of interest in potential treatments for treatment of recurrent ovarian cancer. We outline the current chemotherapeutic agents for treatment of recurrent ovarian cancer below.

We believe that, at least initially, PRR will aim for regulatory approval as a treatment for recurrent ovarian cancer

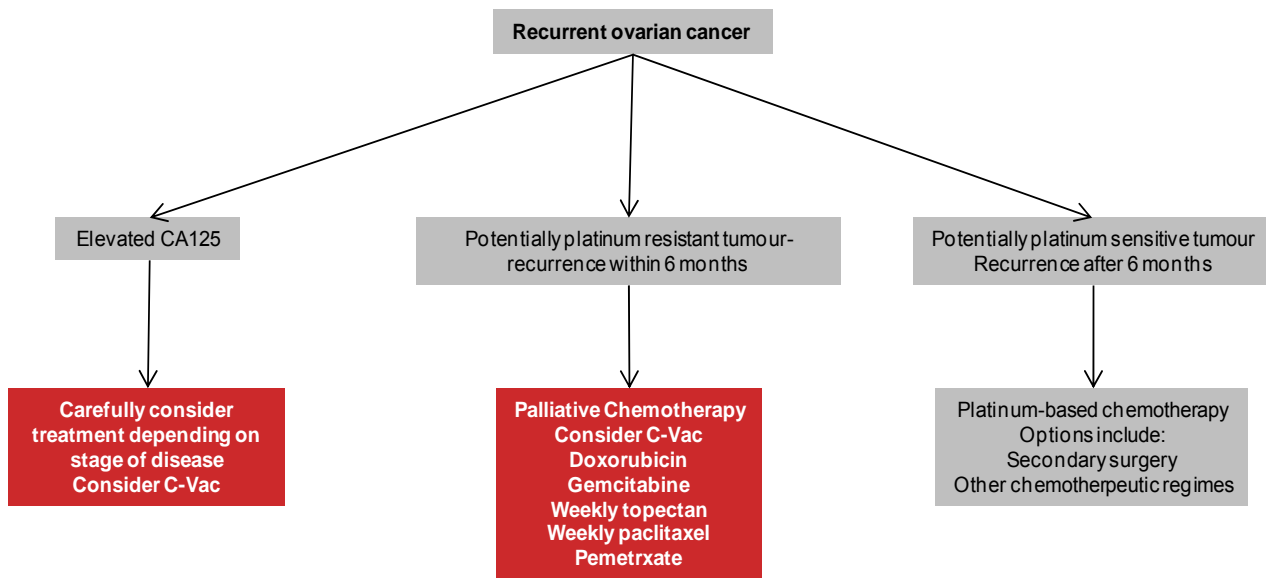
We believe that, at least initially, PRR will aim for regulatory approval as a treatment for recurrent ovarian cancer, rather than as an initial treatment for cancer. We believe PRR's label claim will be for treatment of epithelial ovarian cancer post-remission from first-line chemotherapy. The tumour will have to be positive on immunohistochemistry to Mucin-1.

A. Post surgical treatment of ovarian cancer – primary chemotherapeutic agents are paclitaxel plus carboplatin

Post-surgery, landmark studies have established paclitaxel plus carboplatin as the primary intravenous (IV) chemotherapy treatment strategy for epithelial ovarian cancer. Concurrent with the developments in IV treatment, intraperitoneal (IP) treatment has also been shown to be a potential strategy. We note that Intra-peritoneal chemotherapeutic treatment for ovarian cancer is still off-label.

Traditionally, patients with recurrent platinum sensitive ovarian cancer, defined as a disease-free interval from completion of primary treatment of at least six months, have been re-treated with platinum-based chemotherapy, often in combination with another chemotherapeutic agent. However, cumulative toxicity from primary therapy, specifically neurotoxicity, can preclude re-treatment with paclitaxel and carboplatin.

Fig. 6: Ovarian cancer – recurrent disease algorithm



Source: PubMed

B. Cytoreductive surgery

In patients with recurrent disease, the role of cytoreductive surgery continues to evolve. Several series have suggested the importance of cytoreductive surgery prior to the initiation of second-line chemotherapy.

C. Antiangiogenic Agents

These include:

- **Bevacizumab:** This is a monoclonal antibody that neutralizes the vascular endothelial growth factor (VEGF)-A and thereby inhibits angiogenesis (new blood vessel formation in cancer, a requirement for cancer growth). A preliminary announcement demonstrated a benefit of treatment with bevacizumab but only when bevacizumab is continued as maintenance therapy. Results of this trial presented at the 2010 meeting of the American Society of Clinical Oncology (ASCO) reported a 3.8-month improvement in Progression-Free Survival (PFS). Bevacizumab (Avastin) was recently shown to have single-agent activity against recurrent ovarian cancer with response rates ranging from 15% to 21%, the majority of which occurred following taxane and platinum therapy. It has recently been approved for use in the EU for ovarian cancer;
- **Aflibercept:** This is a potent angiogenesis inhibitor fusion protein. In a phase II trial using, 41% of patients demonstrated stable disease or a partial response to therapy at 14 weeks on the drug; and
- **Sorafenib or Sunitinib:** Currently, a Phase II clinical trial is underway that is testing sunitinib, a therapy approved for use in renal cell cancer in patients with clear cell ovarian cancer. Rather than neutralizing the VEGF molecule, another therapeutic strategy for antiangiogenic agents is to block the VEGF receptor. This can be accomplished with agents such as sorafenib or sunitinib. Numerous protocols

90% of sub-optimally debulked patients and 70% of optimally debulked patients relapse 18 to 24 months following primary treatment

evaluating antiangiogenic agents in combination with cytotoxic chemotherapy for recurrent disease are currently open.

D. mTOR Inhibitors – temsirolimus, everolimus, and deforolimus

Dysregulation of mTOR signalling occurs in many tumours and has been found to be activated in gynaecologic cancers. mTOR Inhibitors interfere with the synthesis of proteins that regulate proliferation, growth and survival of tumour cells. Treatment with temsirolimus leads to cancer cell cycle arrest in the G1 phase, and also inhibits tumor angiogenesis by reducing synthesis of VEGF. Inhibition of mTOR by agents such as temsirolimus, everolimus and deforolimus are in clinical trials. A phase II study for recurrent/persistent ovarian cancers evaluated the use of temsirolimus in recurrent/persistent ovarian and primary peritoneal cancers; results presented at the 2010 meeting of the Society of Gynecologic Oncologists suggested modest activity of weekly single agent temsirolimus in persistent or recurrent disease, with 24.1% PFS at ≥ 6 months.

E. PARP Inhibitors – olaparib

Inhibition of polyadenosine diphosphate [ADP]-ribose polymerase (PARP), a key enzyme in the repair of DNA, may lead to the accumulation of breaks in double-stranded DNA and cell death. Therefore, PARP inhibitors have been developed and are potential agents in the treatment of ovarian cancer. A phase II trial of the oral PARP inhibitor olaparib is an international, multicenter, single-arm study with treatment consisting of continuous use of oral olaparib in BRCA-mutation ovarian cancer patients. The interim analysis from October 31, 2008, showed clinical benefit in 57.6% of patients at 400 mg twice daily.

F. Histone Deacetylase Inhibitors

Aberrant histone modifications, such as hypoacetylation, have been associated with malignancy through the transcriptional silencing of tumour suppressor genes. Belinostat is a histone deacetylase inhibitor (HDAC) that can alter the acetylation level of histone and nonhistone proteins. A phase II study is examining the use of belinostat in combination with carboplatin among patients with recurrent or persistent platinum-resistant disease.

G. Other immunotherapeutic vaccines

Apart from PRR's C-Vac, there are a number of other immunotherapeutic vaccines being developed. Vaccines have been developed to target areas of the CA-125 antigen, a protein produced by most epithelial ovarian cancers. We note that, unlike C-Vac, these vaccines are passive (i.e. they work via the injection of an external antibody):

- **Oregovoma:** This is an immunoglobulin murine monoclonal antibody that binds to CA-125. Retrospective studies and phase II trials showed positive results for the use of oregovomab. However, a randomized controlled trial of patients in first clinical remission showed no benefit over placebo;
- **MUC 16:** A newer antigen being evaluated is MUC 16. The vaccine using MUC 16 as the target is an anti-idiotypic vaccine. It is hoped that such anti-idiotypic vaccines will increase the immune response against the presented antigen. An international randomized phase III trial enrolled patients in a 2:1 fashion to receive this vaccine, and results are pending.

Vaccines have been developed to target areas of the CA-125 antigen, a protein produced by most epithelial ovarian cancers

Size of the ovarian cancer market

The World Health Organisation's International agency for research on cancer estimates the global incidence of ovarian cancer at 235,163 in 2010. There are 21,880 estimated new cases and 13,850 deaths from ovarian cancer in the US alone in 2010.

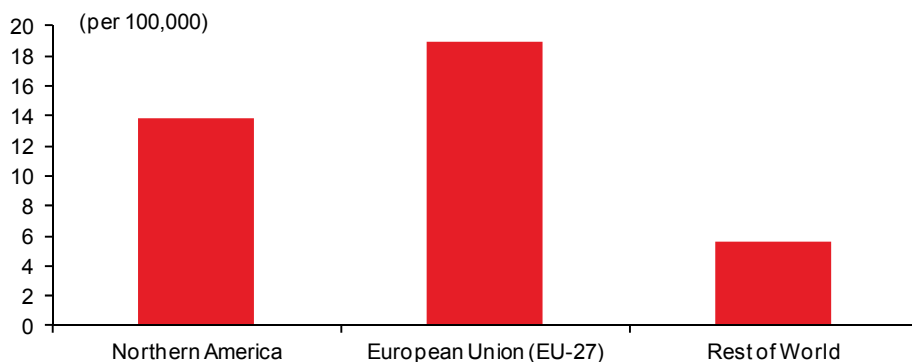
Fig. 7: Incidence of Ovarian Cancer in women aged 0-75yrs

(000s)	2009A	2010A	2011A	2012F	2013F	2014F	2015F	2016F	2017F	2018F	2019F
Northern America	24.3	24.7	25.2	25.6	26.1	26.5	27.0	27.4	27.9	28.4	28.9
European Union (EU-27)	45.2	45.8	46.2	46.7	47.2	47.7	48.2	48.6	49.1	49.5	50.0
Rest of World	160.4	164.7	169.0	173.4	178.0	182.7	187.4	192.0	196.8	201.6	206.5

Source: Globocan

Ovarian cancer is the ninth most common cancer diagnosed in Australian women, and the second most commonly diagnosed gynaecological cancer, according to the ABS.

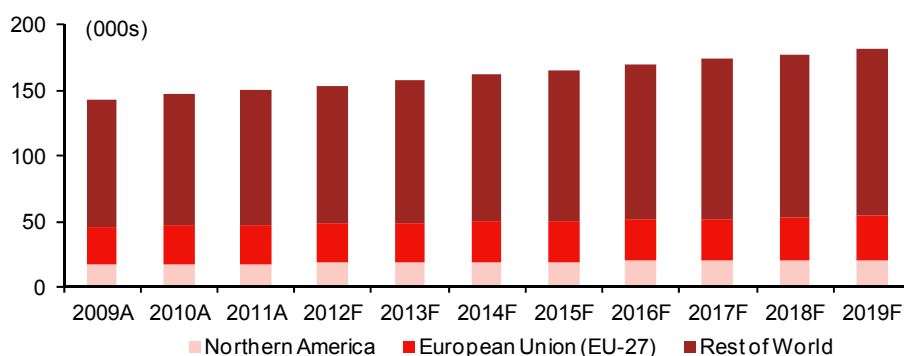
Fig. 8: Ovarian cancer – incidence in different regions



Source: Globocan

Ovarian cancer is the seventh most common cause of cancer death in Australian women. The five-year relative survival rate for Australian women with ovarian cancer has increased significantly, from 33% in 1982-1987 to 40% in 2000-2006. Finally, in Australia, ovarian cancer was the fourth-leading cancer cause of burden of disease for females accounting for 12,900 disability-adjusted life years (DALYs) in 2010.

Fig. 9: Mortality due to Ovarian Cancer



Source: Globocan

Size of the ovarian cancer recurrence market

We have estimated the recurrence of ovarian cancer market, as this is the market in which PRR are attempting to enter. We note that PRR is attempting to address the epithelial ovarian cancer recurrence market. This is seen in the following figure.

In Australia, ovarian cancer was the fourth-leading cancer cause of burden of disease

Fig. 10: Estimating the size of the Ovarian cancer recurrence market for PRR

Estimating the size of the cancer recurrence market	CY11
Number of females with ovarian cancer (EU and US only)	71,404
Of these, 85% of these are epithelial-type ovarian cancer	60,693
Assume surgery is reserved for Stage I,II,III - 65% of cancers	39,451
70% of optimally debulked cancer get recurrence 24 months later, therefore volume of patients with recurrence	27,615
Assume 80% of these patients have MUC-1 type of cancer recurrence	22,092
Assume US\$90K per treatment for C-Vac	
Therefore size of Ovarian cancer recurrence market (US\$m pa)	1988
Assume C-Vac gains 25% market share (US\$m pa)	497

Source: Globocan, Nomura estimates

The World Health Organisation (WHO) predicts that c70,000 females (aged 0-75 years) in the US and EU will be diagnosed with ovarian cancer in 2011. Of which, 85% have epithelial-type ovarian cancer which is targeted by PRR's treatment. We believe approximately 65% or 39,000 patients will be eligible for surgery because we expect their cancer to be diagnosed as stage I-III. Of these, we note that 70% of optimally debulked ovarian cancer patients are predicted to have recurrence 24 months later on the basis of historical recurrence patterns. Of these, we assume that 80% of recurrent ovarian cancer patients would have the MUC-1 type (on the basis of historical incidence rates), which would be sensitive to PRR's C-Vac treatment. If we assume that each treatment would be reimbursed at USD90,000 per annum (in line with reimbursement rates from US public and private insurers for Dendreon's Provenge, which treats prostate cancer), then the potential market size for PRR's C-Vac treatment is in the order of cUSD2bn per annum. Assuming that PRR treats 25% of those females with recurrence of epithelial ovarian cancer, then its potential market is cUSD500mn pa.

PRR – developing its C-Vac vaccine

PRR is developing Dendritic-cell based immunotherapy via its C-Vac vaccine.

What is Dendritic cell based immunotherapy?

Dendritic cells (DCs) can be stimulated to activate a cytotoxic response towards an antigen. DCs are immune cells forming part of the mammalian immune system. Their main function is to process antigen material and present it on the surface to other cells of the immune system (usually T cells). That is, they function as antigen-presenting cells (in PRR's case, ovarian cancer cells). They act as messengers between the innate and adaptive immunity.

An antigen is a substance/molecule that, when introduced into the body, triggers the production of an antibody by the immune system, which will then kill or neutralize the antigen that is recognized as a foreign and potentially harmful invader. These invaders can be molecules, such as pollen or cells, such as bacteria. The term originally came from antibody generator and was a molecule that bound specifically to an antibody, but the term now also refers to any molecule or molecular fragment that can be bound by a major histocompatibility complex (MHC) and presented to a T-cell receptor.

DCs are present in tissues in contact with the external environment, such as the skin (where there is a specialized dendritic cell type called Langerhans cells) and the inner lining of the nose, lungs, stomach and intestines. They can also be found in an immature state in the blood. Once activated, they migrate to the lymph nodes where they interact with T cells and B cells to initiate and shape the adaptive immune response.

In dendritic cell-based immunotherapy, DCs are harvested from a patient. The DCs are then either pulsed with an antigen or transfected with a viral vector. Upon transfusion back into the patient these activated cells present tumour antigen to effector lymphocytes (CD4+ T cells, CD8+ T cells, and B cells). This initiates a cytotoxic (cell killing) response to occur against cells expressing tumour antigens (against which the adaptive response has now been primed). The Dendreon cancer vaccine Provenge is one example of this approach. We explore this in further detail later in this report.

How does PRR's C-Vac ovarian cancer treatment work?

C-Vac cell therapy is a cancer vaccine technology. The C-Vac product consists of an adjuvant, mannan, which is a string of modified mannose (a sugar) units. In a process called apheresis, DCs are removed from the patient's blood.

After a number of DCs are collected, they grow, both in number and maturity, by being cultured with growth factors. Once the target 600 million cells have been achieved, mucin-1-MFP is added. This special protein and sugar complex consists of a protein, Mucin-1, which can be found in great excess in cancer cells, and the mannan sugar. Together, these chemicals form the mannan fusion protein (MFP) that is highly effective at stimulating T cells. The processed DCs are then injected back into the patient's skin where they boost immunity against cancer. C-Vac cell therapy, therefore, uses the attributes of the patient's own body to fight cancer.

In our view, given its nature, the drug will not fail clinical trials because of toxicity – this is a major positive because we believe side-effects are the major reason anti-cancer drugs fail clinical trials.

What is Mucin-1?

Cancer is a disease of the deregulation of tissue growth. Normal cell growth is maintained by the balance between cell proliferation and cell death. In order for a normal cell to transform into a cancer cell, genes that regulate cell growth and cell death must be altered. Mucins have been shown to contain complex associations with various cellular pathways, impacting cell growth, proliferation, and apoptosis. Historically, transformation events in cancer have been defined as initiation events (contributing to the early stages of cancer transition) or progression events (referring to the subsequent transformative processes).

Mucins (MUC) are high molecular weight glycoproteins whose primary functions are to hydrate, protect, and lubricate the epithelial luminal surfaces of the ducts within the

Potential market size for PRR's C-Vac treatment is in the order of USD1.13Bb per annum

human body. MUC1, MUC4, and MUC16 are the well-characterized mucins and have been shown to be aberrantly over-expressed in various malignancies including cystic fibrosis, asthma, and cancer. Recent studies have uncovered the unique roles of these mucins in the pathogenesis of cancer. These mucins possess specific domains that can make complex associations with various signalling pathways, impacting cell survival through alterations of cell growth, proliferation, and death.

MUC1 is a membrane-bound O-glycoprotein that is expressed at the basal level in most epithelial cells. On the other hand, deregulated expression of MUC1 is a prominent characteristic of various types of cancers and inflammatory diseases. In addition, MUC1 mucin has long been viewed as a tumour-associated molecule because of its frequent over-expression and aberrant glycosylation in most carcinomas. MUC1 is over-expressed in >90% of breast carcinomas and frequently in other types of cancer, including ovarian, lung, colon, and pancreatic carcinomas.

How C-Vac works

This is shown below.

Fig. 11: How C-Vac works

Manufacturing of Cvac	White blood cells taken from the patient by apheresis and sent to lab Dendritic cells (DC) separated and cultured to grow 200-600mn DCs DCs are pulsed with antigen Mannan-Mucin-1 Fusion Protein (MFP) Mucin-1 antigen is internalised by the DCs The DCs are then washed and stored in vials (CVac)
Mechanism after injection	Mucin-1 is naturally present on ovarian cancer cells Cvac is injected 6 to 8 in a dose regime Cvac activates the T-cells to produce mucin-1 specific immune response (via cytotoxic T cells) Cytotoxic T-cells target the cancer cells Cytotoxic T-cells destroys cancer cells

Source: Company data

PRR timeline

PRR is currently in Phase IIb trials in the US, and according to the company, plans to start a Phase III trial shortly. A potential timeline for the company is shown below.

Fig. 12: History of PRR and its potential future timelines

Timeline of actual and potential significant events	
Feb-06	Announces Phase I data on C-Vac will be published
May-06	Releases Phase 2a data on C-Vac - response rate of 19% (significant) (Australia)
Oct-06	Announces agreement with Burnet Institute to commercialise new developments
Oct-06	Announces discussing strategic options for development of Cvac in Australia with Cell Therapies
Feb-07	PRR secures worldwide commercialisation rights for the Mucin-1 Antigen for dendritic cell based therapies from Biomira
Sep-07	Final Clinical Study report confirms statistical significance of C-Vac Phase 2a trial
Sep-07	PRR announces that it is unable to secure funds to further clinical trials
Oct-07	Announces appointment of Martin Rogers as a NED
Mar-08	C-Vac Gap analysis report received
Oct-08	PRR completes pre IND meeting with US FDA - plans Phase 2 pivotal trial in the US of C-Vac
Jul-09	PRR submits IND with US FDA
Aug-09	FDA grants approval to commence Phase 2B trial of C-Vac (US)
Jul-10	First patient enrolled for US FDA Phase 2B C-Vac trial
Feb-11	US FDA Phase 2B C-Vac trial - initial safety data released
Feb-11	EMA advises that scientific advice for the Phase III trial has been granted
4QCY11	Enrolment for Phase III trial in C-Vac starts (800 patients)
3QCY11	Completion of C-Vac Phase 2B trial
4QCY12	C-Vac Phase 2B trial results available
1QCY13	Full patient recruitment for Phase III study
2HCY13	Interim data on Phase III trial in C-Vac available
2HCY14	Final data on Phase III trial in C-Vac available
2HCY15	US BLA approved for C-Vac
1HCY16	Sales of C-Vac

Source: Company data, Nomura estimates

The clinical trials for PRR

PRR are progressing through Phase IIb clinical trials, and are planning a Phase III clinical trial. We review the results of each of the trials in turn.

Fig. 13: Status of PRR clinical trials

Phase	Primary endpoint	Secondary endpoint	Number of patients	Nomura Comment
Phase I	Safety data (note only one Ovarian cancer patient)	CA125 levels - for the one ovarian cancer patient. Also assessed anti-tumor efficacy, immune response and procedure feasibility	9	Specifically aims to assess safety
Phase IIa	CA125 response or stabilization in at least 15% patients	Disease progression-free survival, immune response and safety	21	Phase IIa is specifically designed to assess dosing requirements (how much drug should be given)
Phase IIb	Progression free survival	Evaluate host immunologic response to CVac administration	60	Phase IIb is specifically designed to study efficacy (how well the drug works at the prescribed dose)
Phase III	survival and overall survival	Assess quality of life and pharmacoeconomic parameters	800	Phase III studies are randomized controlled multicentre trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment

Source: Company data, Nomura

Phase I clinical trials – C-Vac is safe

In 2006, PRR announced the publication of its Phase I clinical trial with C-Vac Mannan-MUC1 pulsed dendritic cell immunotherapy for adenocarcinoma. The phase I results described in Clinical Cancer Research indicate that the MFP (Mannan Fusion Protein) technology is safe, practical and able to stimulate the right type of immune response for a cancer immunotherapeutic.

Phase IIa C-Vac results in Ovarian Cancer – 19% of patients responded to therapy

In 2007, PRR announced first results for the open label component of its first Phase II trial of C-Vac in ovarian cancer. This was conducted in Australia. The trial objective was to determine the safety of C-Vac, and to monitor CA125 response or stabilization in at least 15% patients.

PRR enrolled 28 patients (21 evaluable) with incurable ovarian cancer (life expectancy at least six months), and rising CA125 levels defined as at least 25% over baseline within one month to confirm the rapidly progressing disease. Patients had received multiple courses of chemotherapy/ radiotherapy. Patients received three injections of C-Vac over a ten week period, followed by four injections at 10 week intervals.

Objectives:

- **Primary:** CA125 response or stabilization in at least 15% patients;
- **Secondary:** Disease progression-free survival, immune response and Safety

C-Vac results

19% of patients responded to therapy (CA-125 reduction or prolonged stabilization) and 47% of patients had disease stabilization (CA-125 remained stable):

- No C-Vac therapy-related toxicity
- Ovarian tumours respond to therapy with CA125 reduction or stabilization
- Progression Free Survival averaged 127 days (95% confidence limits 96 to 219 days)

We note that these were not statistically significant results. Hence, the Phase III clinical trial will assess statistical significance of the response to C-Vac.

Is CA125 a good marker of ovarian cancer relapse?

The FDA recommends that the Gynaecologic Cancer Intergroup (GCIG) guidelines be used for ovarian cancer. The GCIG recommends that for trials of relapsed ovarian cancer the following definition for response according to CA 125 be used in addition to the standard Response Evaluation Criteria in Solid Tumours (RECIST) response criteria.

Evaluation of response according to CA125

The definition of response, according to CA 125, is a response that has occurred if there is at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA 125 only if they have a pretreatment sample that is at least twice the upper limit of normal and within two weeks prior to starting treatment. To calculate CA 125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the normal range of CA 125 levels will not interfere with the response definition.

For each patient, the same assay method must be used and the assay must be tested in a quality-control scheme. Patients are not evaluable by CA 125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. If assessing a therapy that includes two treatment modalities for relapse (e.g., surgery and chemotherapy), we note that any CA 125 response may result from both treatment modalities. CA 125 cannot distinguish between the effects of the two treatments.

A recent validation study of more than 50 potential markers for detecting early signs of ovarian cancer in blood has found that the most accurate marker is CA-125, a protein that is already routinely monitored in women with the disease. Panels of markers tested in the study offered, at best, only marginal improvements in the ability to detect the disease over CA-125 alone. CA-125 remains the single best biomarker for the early detection of this cancer, according to the FDA.

The current FDA recommendation is shown in the following figure.

Fig. 14: CA 125 response in phase II trials – FDA recommendations

CA 125 response in phase II trials - FDA recommendations

Use to support "go/no go" decisions

Define response rate below which further development should be halted

Define minimal acceptable response rate

Define the number of patients required to achieve a 90% power to define response by CA 125.

If CA 125 response rate is greater than minimal acceptable rate, trial continues so that response can be measured with same power by RECIST

CA 125 accurately predicts Progression : Providing

CA 125 measurements same time-point on all arms of randomised trials

If mouse antibodies are used they do not interfere with assay

If biological/ targeted therapy used data from phase 2 trials show acceptable number of discordant results.

If IP therapy given CA 125 levels have returned to within normal range and >28 days from removal of IP catheter.

Use of CA 125 defined progression in clinical trials: recommendations

Should be incorporated into trial protocols of first line and relapse therapy of ovarian cancer.

Progression according to RECIST always takes precedence

Use of CA 125 will shorten progression free survival

Reduces number of CT scans required during follow up.

Source: US FDA

Phase IIb C-Vac trial – trial ongoing

There is an ongoing Phase IIb trial in 60 patients for ovarian cancer patients after a successful first- or second-line therapy. This trial is recruiting patients in the US and Australia in order to:

- Assure comparability of multiple manufacturing centres;
- Confirm safety and tolerability established in earlier trials;
- Compare C-Vac to standard of care in terms of progression-free survival (PFS); and
- Confirm host immunologic response to C-Vac therapy

PRR Phase 2B study design

The PRR Phase 2B study objectives are to determine the safety and efficacy of C-Vac compared with Standard of Care in ovarian cancer patients who are in remission after the first- or second-line therapy.

Primary Objectives:

- To confirm the safety of administering C-Vac in this population; and
- To determine the effects of C-Vac on progression-free survival (PFS).

Secondary Objectives:

- To determine overall survival (OS) for recurrent ovarian cancer patients who receive C-Vac after achieving remission in the first or second-line setting; and
- Evaluation of host immunologic response to C-Vac administration.

Patients will receive vaccinations every four weeks for 24 weeks followed by injections every eight weeks for an additional 24 weeks. The standard of care for placebo patients is no intervention – patients will be under observation, no cancer treatment will be given to this group. The Phase 2B trial will likely report in 1QCY13. This is seen in the following figure.

We note that, much like the Phase IIa trial, this Phase IIb trial is not expected to demonstrate statistical significance. Hence, the Phase III clinical trial will assess statistical significance of the response to C-Vac.

Fig. 15: PRR Phase IIb – trial outline

Estimated Enrollment:	60
Study Start Date:	Feb-10
Estimated Study Completion Date:	Feb-13
Estimated Primary Completion Date:	February 2013 (Final data collection date for primary outcome measure)

Note: we believe this would be the final date of completion – PRR expect the trial to finish faster than this
Source: clinicaltrials.gov

Phase III clinical trial

PRR has announced that a Phase III trial for ovarian cancer patients in remission is planned to commence by 4QCY11. This will be performed in Europe, the US, and Australia. It consists of 800 patients, and will be a randomized, double-blinded, efficacy trial. PRR undertook a capital raising to at least partially fund this trial, which is to cost AUD40-55mn, according to the company. We expect an announcement on the start of the Phase III clinical trial in the near term.

Its aim is to definitively establish survival benefit, namely progression free survival (PFS) and overall survival (OS). It will also assess quality of life and pharmaco-economic parameters. Overall, it is expected by the company that this trial will support marketing authorisations globally. The interim data analysis set for 2HCY13.

Fig. 16: PRR – outline of clinical trials in C-Vac

Phase	Primary endpoint	Secondary endpoint	Number of patients	Statistically significant results?	Time to report results	Nomura Comment
Phase I	Safety data (note only two ovarian cancer patients)	CA125 levels. Also assessed anti-tumor efficacy, immune response and procedure feasibility	9	No	Reported	Specifically aims to assess safety
Phase IIa	CA125 response or stabilization in at least 15% patients	Disease progression-free survival, immune response and safety	21	No	Reported	Phase IIa is specifically designed to assess dosing requirements (how much drug should be given)
Phase IIb	Progression free survival	Evaluate host immunologic response to CVac administration	60	Unlikely, given Phase IIa results	1HCY2013	Phase IIb is specifically designed to study efficacy (how well the drug works at the prescribed dose)
Phase III	Progression free survival and overall survival	Assess quality of life and pharmaco-economic parameters	800	Awaiting	2HCY14 (for final results)	Phase III studies are randomized controlled multicentre trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment

Source: Nomura estimates, company data

Pilot commercialisation program ... revenues from CY12?

In May 2011, PRR announced that Dubai Healthcare City (DHCC) has granted approval for the marketing and distribution of C-Vac in DHCC. Subject to Prima finalising its Australian manufacturing license (which is due next month) and a test run to show logistical chain of custody from Dubai to Australia and back, the first sales of C-Vac in DHCC could be earned before the end of 2011. PRR currently has about 10 patient enquiries regarding treatment via the DHCC.

C-Vac will be available in DHCC through PPR's partnership with The City Hospital. Prima and The City Hospital have signed a Memorandum of Understanding laying out the terms and conditions by which C-Vac will be available at The City Hospital. A further agreement between the parties is to be signed in combination with full regulatory approval for C-Vac.

We believe other countries may approve C-Vac as a 'blood product', prior to full regulatory approval by the US and EU.

Examination of patents

C-Vac has exclusively licensed four "families" of patent applications from the Austin Research Institute in Melbourne. Each family consists of applications in major countries, including the US, Europe, Japan, Australia and Canada:

- **Family 1** is directed to the mannan adjuvant – antigen conjugate, used to prime the immune system's dendritic cells;
- **Family 2** is directed to cancer antigens believed to be capable of stimulating anti-cancer immune responses. These are synthetic proteins that are based on MUC 1;
- **Family 3** is directed at the procedure and immune cell product used by C-Vac to deliver its immunotherapy; and
- **Family 4**, like family 2, is directed to cancer antigens, specifically other immunogenic portions of MUC1.

PRR will have up to 10 years of marketing exclusivity, should the drug get to the market

This is seen below.

Fig. 17: C-Vac patent family

Patent	Family	Status	Expiry
C-Vac Mannan fusion	Composition of matter patent –Mucin-Mannan conjugates, antigen carbohydrate compounds, or mucin-1 derived antigens and their use in immunotherapy	Granted in Australia, Canada, Japan (x2), USA (x2), UK, Italy, France, Germany, Ireland. Application allowed in the USA	2014
Mimics	Mucin -1 mimicking peptides and their use in cancer immunotherapy	Granted in Australia, New Zealand, USA, Japan, UK, Italy, France, Germany, Switzerland. Application allowed in Canada	2016
Ex vivo cell therapy	Method of producing dendritic cells pulsed with MFP (family 1).	Granted in Australia, Austria, Belgium, Denmark, France, Germany, Italy, Ireland, Granted in Australia, Austria, Belgium, Denmark, France, Germany, Italy, Ireland, Japan, Luxembourg, Spain, Sweden, Switzerland, Netherlands, UK. Applications pending in the USA, and allowed in Canada	2018
Non-VNTR regions	New immunogenic regions of Mucin-1 and their use in cancer immunotherapy	Granted in Australia and the USA. Applications pending in Europe, Canada, and Japan.	US: 2014 ROW: 2021

Source: Company data

The granted patents protect cancer antigens which C-Vac can use in the commercialisation of its immunotherapy program. The patent will remain in force until at least 2018. PRR hopes to be granted a five-year extension to this patent.

C-Vac has received Orphan Drug Designation from the US Food and Drug Administration in September 2010 and European Medicines Evaluation Agency in June 2010. This means that PRR will have 10 years of marketing exclusivity in the US and seven years marketing exclusivity in the EU, should the drug get to market.

CVac has a relatively long lifecycle

CVac has a patent protection through December 2018 – this may extend to 2023 via Hatch-Waxman extension. Orphan Drug Designation gives a seven-year or 10-year protection from date of marketing launch. However, given the nature of the product – a cell-based patient-specific therapy whose manufacture involves considerable proprietary know-how and coordination, barriers to eventual generic entry may be high (even relative to existing biologics).

Other Products – the oral HPV vaccine

Most vaccines are not given orally, as they are degraded by the protein breakdown and digestive processes in the gut. However, there are also some fundamental immunological reasons why oral vaccines are less of a threat to Nanopatch than one might expect.

Orally delivered vaccines are processed and presented by the digestive tract's immune system, often referred to as the gut-associated lymphoid tissue (GALT). The GALT is a complex system consisting of inductive sites (where antigens are encountered and responses are initiated) and effector sites (where local immune responses occur) linked by a homing system, whereby cells induced by antigen in the GALT migrate to the circulation and, subsequently, colonize the mucosa. As a result, oral vaccination induces immune responses locally in the gut and less so immune responses at other sites or in the blood. Accordingly, studies of oral vaccines have focused on pathogens that enter the body through mucosal surfaces and cause diseases of the intestinal, respiratory and genital tracts. There has been relatively less focus on the development of oral vaccines against pathogens that enter the body through routes other than the mucosa, such as blood, and that may manifest disease by colonization of non-mucosal tissues and organs. There are a number of compelling reasons why oral vaccines for many diseases remain a major challenge and will be so over the near to medium term.

A minority of vaccines that are licensed for human use are administered orally, including polio, cholera, typhoid, rotavirus and adenovirus vaccines. All of these oral vaccines are designed to prevent diseases contracted through mucosal surfaces and are composed of either live-attenuated viruses/bacteria or killed whole cells. By contrast, there has been relatively little progress in the clinical development of subunit oral vaccines, particularly for non-mucosally transmitted pathogens. The availability of a range of novel delivery systems, as well as the development of mucosal adjuvants and genetically modified foods, has provided potential for the future development of subunit oral vaccines, but with little progress. A detailed understanding of the mechanisms of oral immunization is critical for the design of effective oral vaccines; however, as for vaccines in general, such understanding has remained elusive and vaccine formulation still remains largely empirical.

A major concern regarding oral delivery is the possibility of inducing oral tolerance, whereby oral delivery of an antigen would prevent systemic responses on subsequent exposure to the same antigen. Such oral tolerance has been extensively studied in animal models including mice, rats and guinea pigs. Other species appear to be less prone to the development of systemic non-responsiveness. Although tolerance is the default response of the intestinal immune system, studies showed that it does not occur every time the antigen is fed, but depends on a multitude of factors, such as the nature, size and dose of the antigen, co-administration of adjuvant and host-specific factors. Thus, the potential for an oral vaccine to induce oral tolerance will need to be assessed carefully by trials.

For attenuated live vectors, there is an inherent danger that live vaccines may revert back to virulence or retain sufficient virulence to become pathogenic in immune-compromised individuals, particularly if the attenuated organisms survive long enough to pass from person to person (as they may do with oral administration). We note that a significant proportion of the world's population, particularly those in some African countries, show levels of immunosuppression due to HIV infection; thus, special caution is required when devising and performing a clinical trial to test a new attenuated organism vaccine in these populations. In addition, more information is required regarding the efficiency of such vaccines in populations with significant levels of pre-existing immunity to the carrier.

Listed comparables

- **ImmunoCellular Therapeutics** (IMUC OB, not rated): This is a clinical-stage biotechnology company that is focused on developing immune-based products to treat and diagnose cancer. IMUC are developing active immunotherapies that target not only regular tumour cells, but also the cancer stem cells believed to cause cancer growth and recurrence. IMUC are also identifying and developing monoclonal antibodies that may be used to treat and diagnose a wide range of cancers. IMUC's advanced clinical programs are in glioblastoma multiforme, an advanced stage of brain cancer. It is in Phase II with this indication.
- **Dendreon** (DNDN, not rated): Listed on the Nasdaq, with a market cap of USD1.7bn, Dendreon is developing therapeutic vaccines that help the body's immune system fight cancer by targeting dendritic cells, which initiate an immune response to disease-causing antigens. Its' leading candidate, Provenge (sipuleucel-T), a therapeutic vaccine that targets prostate cancer, received FDA approval in 2010. We go into more details on this company further in the note.
- **Oncothyreon** (ONTY US, not rated): is based in Seattle, Washington, and is a biotechnology company dedicated to the development of oncology products. ONTY are currently developing multiple therapeutic candidates designed to target cancer. ONTY's pipeline includes both synthetic vaccines and small molecules for a variety of cancer indications. ONTY's relevant clinical trials are around Stimuvax (a BLP25 liposome vaccine). Currently in Phase 3 Trials, Stimuvax is a cancer vaccine designed to induce an immune response to cancer cells that express Mucin-1 (MUC1). Stimuvax works by stimulating the body's immune system to identify and destroy cancer cells expressing MUC1. Stimuvax is being developed by Merck KGaA (MRK GY, BUY, EUR 67.60) of

Darmstadt, Germany under a license agreement with Oncothyreon. Merck is currently conducting two Phase 3 trials of Stimuvax, called: 1) START – Stimulating Targeted Antigenic Responses to Non Small Cell lung Cancer and 2) INSPIRE (Stimuvax trial In Asian NSCLC Patients: Stimulating Immune Response) a trial of Stimuvax in Asian patients with advanced non-small cell lung cancer (NSCLC).

- **Bavarian Nordic** (BAVA DC, not rated) is a biotechnology company developing and producing vaccines. The company's clinical pipeline targets cancer and infectious diseases, and includes seven development programmes. Relevant programmes include: 1) Prostavac (pre-phase III), a therapeutic vaccine for advanced prostate cancer that is being developed under a collaboration agreement with the National Cancer Institute, and 2) CVAC-301 – this is a cancer immunotherapy product candidate incorporating two antigens (CEA and MUC-1) that are over expressed in other major cancers, including breast, lung, and ovarian. CVAC-301 is currently the subject of an NCI-funded, randomized Phase 2 study of docetaxel alone or in combination with CVAC-301 in metastatic breast cancer with data expected in the first half of 2012. Both Prostavac and CVAC-301 are prime-boost vaccines, sequentially combining two different poxviruses (vaccinia and fowlpox).

Management

There is a significant experience in the management team. We provide an outline of the management team below.

Fig. 18: PRR management

Martin Rogers	Chief Executive Officer	Mr Rogers is Managing Director and Chief Executive Officer of Prima BioMed. He has degrees in science and chemical engineering and is currently a member of the management committee of the National Breast Cancer Foundation.
Matthew Lehman	Chief Operating Officer	Mr. Matthew Lehman is Chief Operating Officer at PRR, a Member at European Business Association, and a Member at Association of Clinical Research. Mr. Lehman was previously employed as Chief Operating Officer by SPRI Clinical Trials Global LLC and Professionals. Operations Director by Social Psychiatry Research Institute. He received his undergraduate degree from the University of Louisville and a graduate degree from Columbia University.
Ian Bangs	Chief Financial Officer	Mr. Ian Bangs is Chief Financial Officer at PRR and Chief Financial Officer at Air Change International Ltd. Mr. Bangs was previously employed as Chief Financial Officer & Secretary by LandMark White Ltd. and Secretary by IFC Capital Ltd.
Neil Frazer	Chief Medical Officer	Dr. Neil M. Frazer, MD, is Executive Director & Chief Medical Officer at PRR and Chief Medical Officer at Chimerix, Inc. Dr. Frazer was previously employed as an Advisor by 3V SourceOne Capital LLC. He received his undergraduate degree from The University of Edinburgh.
Sharron Gargosky	Senior Vice President-CVac Clinical Programs	Dr. Sharron E. Gargosky is Senior Vice President-CVac Clinical Programs at PRR, Chief Scientific Officer at Pulse Health LLC, and Chief Scientific Officer at Hyperion Therapeutics, Inc. Dr. Gargosky was previously employed as Clinical Director by Pharmacia AB, Clinical Director by Pharmacia Corp., Executive Director-Research & Development by Medicis Pharmaceutical Corp., Executive Director-Research & Development by Ucylyd Pharma, Inc., a Professor by Oregon Health Sciences University, and Vice President-Business Development by Diagnostic Systems Laboratories, Inc. She received her undergraduate degree from the University of Adelaide and a doctorate degree from the University of Adelaide.
Marc Voigt	General Manager, European Operations	Mr Voigt joined Prima BioMed's management team in 2011 as the General Manager of the company's European operations at Prima BioMed GmbH. He previously worked as an investment manager for Allianz Insurance biotech venture fund, and as a personal assistant to a member of the Executive Board of Allianz Insurance. In the biotech sector he held the positions of CFO/CBO at Revotar Biopharmaceuticals AG and Medical Enzymes AG. He has a Masters Degree in Business Administration from the Freie University of Berlin.

Source: Company data

In terms of management, in our view the recent direction of the company has been impressive. We believe the clinical team is of a high standard. We believe this increases the possibility of a properly designed trial process and this will support registration of the product. PRR has an impressive Board of directors as well, in our view.

Fig. 19: PRR Board of directors

Lucy Turnbull	Chairman	Ms. Lucy H. Turnbull is Chairman at PRR and Deputy Chairman at The Committee For Sydney. She is on the Board of Directors at Cancer Institute NSW, Independent Studies, Sydney Metropolitan Development Authority, University of Sydney, Biennale of Redfern-Waterloo Authority, Centre for Sydney, and Redfern Foundation. Ms. Turnbull was previously employed as Chairman by Sydney Childrens Hospital Foundation. She also served on the board at Sydney Cancer Centre Foundation.
Richard Hammel	Non-Executive Director	Dr. Richard J. Hammel is Non-Executive Director at PRR and Founding Partner at Propharma Partners International, Inc. Dr. Hammel was previously employed as Vice President-Commercial Development by Connetics Corp. and VP-Business Development, Sales & Marketing by Matrix Pharmaceuticals, Inc. He also served on the board at Glaxo, Inc.
Neil Frazer	Chief Medical Officer	Dr. Neil M. Frazer, MD, is Executive Director & Chief Medical Officer at PRR and Chief Medical Officer at Chimerix, Inc. Dr. Frazer was previously employed as an Advisor by 3V SourceOne Capital LLC. He received his undergraduate degree from The University of Edinburgh.
Yue-Ling Albert Wong	Deputy Chairman	Mr. Yue-Ling A. Wong is Non-Executive Chairman at Cabral Resources Ltd., Deputy Chairman at PRR, Practitioner Member at Stockbrokers Association of Australia, Non-Executive Director at Lahoca Resources Pte Ltd., Chairman at Winmar Resources Ltd., and Governor-Science Foundation at University of Sydney. He is on the Board of Directors at Ian Thorpe's Fountain For Youth and UNSW Foundation Ltd. Mr. Wong was previously employed as Non-Executive Chairman by RIMCapital Ltd., a Member by ASX Ltd., Founding Director by Gujarat NRE Resources NL, Founding Director by Pluton Resources Ltd., and a Principal by Intersuisse Ltd. He received his undergraduate degree from The University of New South Wales.
Martin Rogers	Chief Executive Officer	Mr Rogers is the Managing Director and Chief Executive Officer of Prima BioMed. He has degrees in science and chemical engineering and is currently a member of the management committee of the National Breast Cancer Foundation.

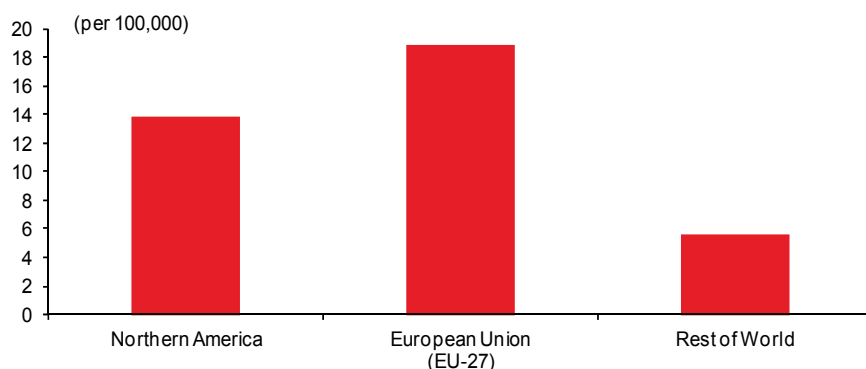
Source: Company data

Valuation of the technology

We have evaluated PRR's ovarian cancer opportunity. There are a number of variables in this analysis. These include:

- **Timeline for getting to market:** We assume the ovarian cancer opportunity would get to the market in FY16F in the US, and will get to the market in FY16F in the EU;
- **Size of the potential market:** We assume PRR would, at least initially, address the US and EU markets for ovarian cancer, given their significant size and relatively established nature. Over time, we believe PRR will also attempt to address the markets in Canada, Australia and Japan. The numbers of females aged 0-75 years with ovarian cancer are shown in the following figure.

Fig. 20: Incidence of Ovarian cancer



Source: WHO

Within the US and EU, PRR is aiming to address the 80% of these who have recurrent, Mucin-1 type epithelial ovarian cancer. We assume a maximum penetration rate of this subset of 25%. The assumed rate of patient take-up is critical to PRR's equity valuation given its sensitivity to this factor, yet the rate of patient take-up is very difficult to predict. We assume PRR treats 194 patients in FY16F (its first year in the market) and that the number of treatments increases by a CAGR of 80% over the first five years to 2,057 patients. This equates to 8.4% penetration of the US/EU markets. We then assume that the treatment CAGR reduces to 30% per annum over the next five years to 7361 patients by its tenth year in the market. This equates to 25% penetration of the US/EU markets. During this period, we expect that PRR to consider targeting geographic markets other than those mentioned above. We have not factored this in our forecasts.

Fig. 21: Potential treatment market

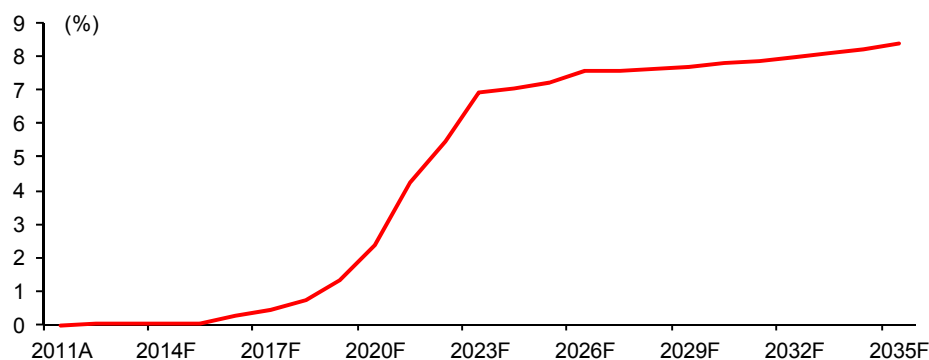
	2009A	2010A	2011A	2012F	2013F	2014F	2015F	2016F	2017F	2018F	2019F	2020F
Clinical Trial Phase	I	Ila	Ilb	Ilb/III	III	III	Filing	Yr 0	Yr 1	Yr 2	Yr 3	Yr 4
Probability of success (%)	13.4	17.4	21.4	61.2	61.2	61.2	90	100	100	100	100	100
Market penetration of C-Vac (%)												
Northern America		0.0	0.0	0.0	0.0	0.0	0.0	0.8	1.4	2.6	4.7	8.4
European Union (EU-27)		0.0	0.0	0.0	0.0	0.0	0.0	0.8	1.4	2.6	4.7	8.4
Rest of World		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
Number of women treated by C-Vac												
Northern America		0	0	0	0	0	0	66	120	220	403	737
European Union (EU-27)		0	0	0	0	0	0	118	215	390	708	1287
Rest of World		0	0	10	10	10	10	10	14	18	24	32
World		0	0	10	10	10	10	194	348	628	1135	2057

Source: Nomura estimates

In developing our model, we assume that PRR develops and markets C-Vac without the use of a strategic partner. We will update our model should PRR enter into a commercial arrangement with another party.

Fig. 22: Forecast global market penetration of C-Vac within ovarian cancer segment

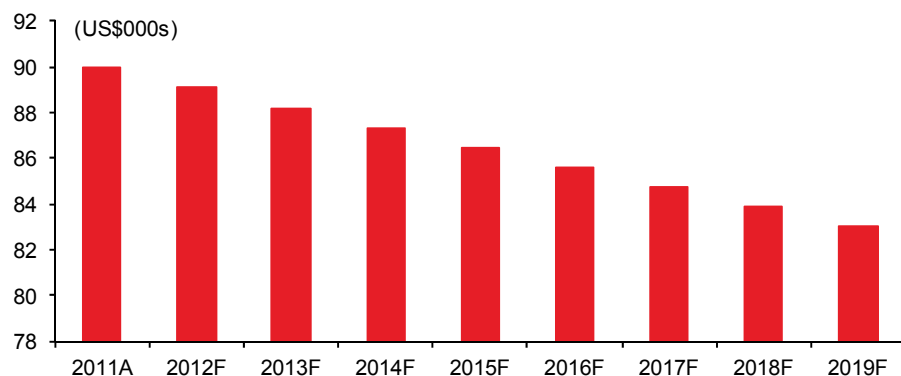
Assumes peak penetration of 25% in US and EU markets



Source: Nomura estimates

- **Number of injections:** We assume that one treatment series would be required to treat the ovarian cancer;
- **Reimbursement:** We assume a treatment cost per injection of USD90,000. PRR's closest comparable is Dendreon's Provenge (an immunotherapeutic for prostate cancer) which is reimbursed at USD93,000 per treatment, so we believe our assumption is not unreasonable. We assume this price will decline 1% per year;

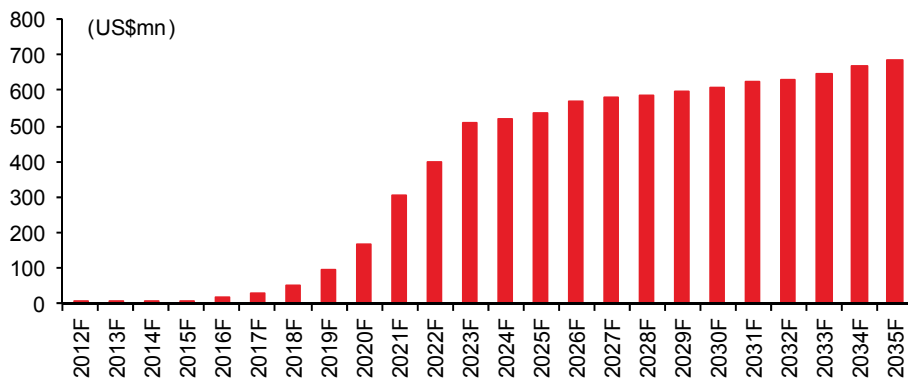
Fig. 23: C-Vac pricing



Source: Nomura estimates

- **COGS per treatment:** Initially, we estimate COGS per CVAC treatment initially at USD25K per treatment. We assume growth in COGS per treatment would be flat during the clinical trials phase (FY12F-FY16F). By FY17F onwards, we assume COGS per CVAC treatment at USD15K per treatment on the basis that PRR improves efficiency and utilises automation for its commercialisation of CVAC. We note that PRR management aims to decrease COGS to cUSD10K per treatment over the longer term;

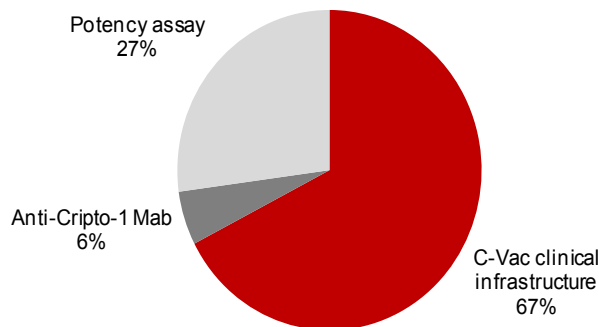
Fig. 24: PRR – revenues from C-Vac



Source: Nomura estimates

- **Other operating expenses:** PRR is targeting expenditure of AUD1.4-1.7mn per month during the course of its phase III clinical trial. We forecast AUD1.5mn for FY12F and FY13F. PRR expects to invest AUD50 to 100mn over the next five years. In our model, we estimate PRR will spend AUD84mn over the next five years. Given its cash balance was AUD56mn as at 30 June 2011, this rate of cash burn will necessitate another capital raising in twelve to 24 months time;
- **Research & development expenditure:** As PRR enters phase III clinical trials, we expect R&D expenditure will increase from historical levels and largely be directed towards C-Vac and clinical infrastructure. We forecast the company will spend AUD11mn in FY12F and a further AUD10mn in FY13F. This compares to PRR's R&D expenditure of AUD9.2mn in FY11A. A breakdown of research & development expenditure is shown below.

Fig. 25: FY11A research & development expense breakdown



Source: Company data

- **Capital requirement:** We assume a future capital raising of AUD50mn in FY13F;
- **Hedging:** PRR has hedging contracts to cover 75% of its cashflows for a 12-month period and 50% over a 24-month period. Currently, its cashflows are hedged at 73c for the euro and 1.02 for the US dollar. PRR estimates the cost of hedging its exchange rates is AUD500K;
- **Exchange rate:** We assume exchange rates in line with the Nomura's house view. For FY12F, the relevant exchange rates are: 1) AUD/USD – 1.06, 2) AUD/€ – 0.74; 3) €/USD – 1.44. Our long-term rate for the AUD/USD exchange rate is 0.81;
- **Discount rate:** In line with PRR's WACC, we use a WACC of 16.05% for this scenario analysis. Our assumptions include: 1) Equity beta – due to its inherent risks, PRR has a higher beta than most other industrial companies. We assume that the company's equity (and asset) beta is 1.80, in line with the average beta for higher-risk biotech opportunities; 2) Nominal long-run growth rate – given the potentially high growth rate of this business, and in line with those of other high-growth companies in the market, we assume a nominal long-run growth rate of 5% and a real long-run growth rate of 2.5%; and
- **DCF per share:** On the basis of the above, the discounted cashflow valuation per share for PRR's ovarian cancer opportunity is AUD0.50.

Other financial aspects of the company

- **Deferred tax assets not recognised:** Although recovery of the potential tax benefit is uncertain, PRR had accrued AUD19.5mn in potential tax benefit as at 30 June 2011. The Federal Government Bills creating the 45% tax credit on research and development expenditure has been passed recently. The tax credit legislation will provide a 45% refundable tax credit for companies with total revenue less than AUD20mn a year and a 40% non-refundable tax credit to all other companies. We believe that, as an Australian company, PRR may be able to benefit from this. We have not included this in our forecasts;
- **Springtree convertible loan facility:** In January 2011, PRR terminated its convertible loan facility provided by Springtree Special Opportunities Fund LP. The loan facility has

served its purpose as a funding vehicle whilst PRR was in its earlier stage of development. Given PRR completed its AUD44.7mn equity raising during FY11A, we believe it has sufficient funds to operate for the next 12 to 18 months at its targeted cash burn of AUD1.4-1.7mn per month. The structure of the convertible loan was such that PRR would receive AUD700K per month in funding for which it would issue PRR shares at a 10% discount to the five-day volume weighted average share price (VWAP). A change in accounting treatment detailed in the restatement to the FY11 accounts has given rise to “a re-measurement of the fair value of shares and options issued to repay the loan, commitment options and collateral shares issued have been expensed over the period of the facility as finance expenses. In addition, loan transaction costs have been amortised over the period of the facility”. The net impact of these restatements has been to increase non-cash finance costs by AUD5.2mn in FY11A and AUD5.2mn in FY10A. According to the company, these costs may give rise to future tax benefit amounting to AUD9mn subject to an ATO ruling; and

- **EU grant:** PRR was awarded a grant to help fund the C-Vac clinical programme in Europe. In August 2011, PRR was awarded a EUR4.1mn grant by the German state of Saxony. The grant came from an R&D grant programme, which was designed to provide funding for specific projects which demonstrate the potential to further economic development in Saxony. The grant was provided by the State Ministry for Higher Education, Research and the Arts of Saxony. Prima and the Fraunhofer Institute of Cell Therapy and Immunology (Fraunhofer IZI) submitted a joint proposal for the grant, to cover the costs of C-Vac materials and manufacturing, plus staffing costs in Saxony and some clinical procedure costs of the European component of C-Vac’s trial process. Prima and Fraunhofer will be reimbursed for eligible costs as they are incurred during the project. Funds under the grant are provided by the European Union and the state of Saxony.

Major comparable – Provenge by Dendreon (DNDN US, not rated)

Listed on the Nasdaq with a market cap of USD1.7bn, Dendreon is developing therapeutic vaccines that help the body’s immune system to fight cancer by targeting dendritic cells, which initiate an immune response to disease-causing antigens. Its leading candidate, Provenge (sipuleucel-T) is a therapeutic vaccine that targets prostate cancer, and received FDA approval in 2010. Dendreon also has a therapeutic vaccine called Neuvenge in phase I trials, as a treatment for breast, colorectal, and ovarian cancers; and it has research programmes investigating cancer-fighting monoclonal antibodies and small molecule drugs.

What are PRR’s similarities with Dendreon?

C-Vac is based on the same cellular technology as Dendreon’s Provenge. We would argue that the FDA approval of Provenge for asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer validates the underlying science behind C-Vac.

Difference between DNDN and PRR

Dendreon effectively has a purification strategy – this removes already existing dendritic cells (DCs) from the circulation. However, PRR, in common with many others, uses a mononuclear white cell collection to get a large number of monocytes, which it then converts into DCs through expansion culture using cytokines known as IL4 and GM-CSF.

We believe some industry players have invested more in automation upfront to reduce the risk of product changes further down the track when they move to automated platforms.

Sipuleucel-T

Prostate cancer is the most common non-cutaneous cancer among men in the US and is the second-leading cause of death from cancer in men, according to the CDC. Localized prostate cancer may be cured with surgery or radiation therapy, but the disease recurs in approximately 20 to 30% of patients. Androgen-deprivation therapy, the most common

treatment after recurrence, is effective, but the disease eventually progresses in most patients who receive such treatment. For men with metastatic castration-resistant prostate cancer, the median survival in recent phase 3 studies has ranged from 12.2 to 21.7 months. A chemotherapeutic agent, docetaxel, is the only approved therapy that has been shown to prolong survival among men with this condition, conferring a median survival benefit of 2 to 3 months, compared with mitoxantrone and prednisone. Combination therapy with mitoxantrone plus a glucocorticoid has been reported to provide palliation but no survival benefit, as compared with a glucocorticoid alone.

Provenge (sipuleucel-T) is an autologous cellular immunotherapy for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

Sipuleucel-T is an active cellular immunotherapy, a type of therapeutic cancer vaccine, consisting of autologous peripheral-blood mononuclear cells (PBMCs), including antigen-presenting cells (APCs), that have been activated *ex vivo* with a recombinant fusion protein (PA2024). PA2024 consists of a prostate antigen, prostatic acid phosphatase that is fused to granulocyte-macrophage colony-stimulating factor, an immune-cell activator.

Phase III clinical trial in sipuleucel-T

In this double-blind, placebo-controlled, multicenter phase 3 trial, investigators randomly assigned 512 patients in a 2:1 ratio to receive either sipuleucel-T (341 patients) or placebo (171 patients) administered intravenously every two weeks, for a total of three infusions. The primary end point was overall survival, analysed by means of a stratified Cox regression model adjusted for baseline levels of serum prostate-specific antigen (PSA) and lactate dehydrogenase.

In the sipuleucel-T group, there was a relative reduction of 22% in the risk of death compared with the placebo group (hazard ratio, 0.78; 95% confidence interval [CI], 0.61 to 0.98; P=0.03). Relative risk reduction is defined as the proportion of the risk removed by treatment: the reduction absolute risk reduction divided by the initial risk in the control group; usually expressed as a percentage.

This reduction represented a 4.1-month improvement in median survival (25.8 months in the sipuleucel-T group vs. 21.7 months in the placebo group). The 36-month survival probability was 31.7% in the sipuleucel-T group versus 23.0% in the placebo group.

The use of sipuleucel-T prolonged overall survival among men with metastatic castration-resistant prostate cancer. No effect on the time to disease progression was observed.

Fig. 26: Comparison of C-Vac and sipuleucel-T (Provenge)

	C-Vac	sipuleucel-T
Clinical stage	2	2
Relative risk of death reduction (%)	19	19
P-value	not statistically significant	0.03
Improvement in median survival (months)	4.1	4.1

Source: Company data

Getting FDA approval – relevant for C-Vac's path to market

In April 2009, Dendreon announced that the pivotal Phase 3 IMPACT study of Provenge (sipuleucel-T) in men with advanced prostate cancer met its primary endpoint of improving overall survival compared to a placebo control. The magnitude of the survival difference observed in the intent to treat population resulted in the study successfully achieving the pre-specified level of statistical significance defined by the study's design. The safety profile of Provenge appeared to be consistent with prior trials. This was conducted under a Special Protocol Assessment agreement with the U.S. Food and Drug Administration (FDA).

Clinical Trial Results Supporting U.S. Food and Drug Administration (FDA)

Approval

Three Phase 3 studies involving 737 patients were submitted to FDA to support licensure. The pivotal study was the Phase 3 IMPACT (Immunotherapy for Prostate

AdenoCarcinoma Treatment) trial (D9902B), a 512-patient, multi-center, randomized, double blind, placebo-controlled study that evaluated men with asymptomatic or minimally symptomatic, metastatic Castration-Resistant Prostate Cancer (CRPC). Provenge extended median survival beyond two-years, demonstrating a median improvement of 4.1 months compared to the control group (25.8 months versus 21.7 months). Overall, Provenge reduced the risk of death by 22.5 percent compared to the control group (HR=0.775). Results from the similarly designed Study D9901 in asymptomatic metastatic CRPC also demonstrated a survival advantage of similar clinical magnitude as the IMPACT study.

US reimbursement – relevant for C-Vac’s path to market

In November 2010, the US Centers for Medicare and Medicaid Services (CMS) panel backed Dendreon's cancer vaccine for reimbursement for the use specified on its label. The vaccine has the FDA's blessing for use in advanced prostate-cancer patients whose disease has resisted standard hormone treatment. The panel affirmed that Provenge offers a survival benefit, awarding the treatment a 3.6 rating on a 5-point scale.

Most prostate cancer patients are over 65, and hence covered by Medicare, and allowing off-label use could increase the market size for the USD93,000-per-patient drug. Each infusion of Provenge will cost USD31,000, bringing the full cost of treatment for three infusions to USD93,000. The drug costs about USD23,000 per month of life extension, based on the Phase III study that found the drug extended life by 4.1 months. Dendreon spent about USD1bn developing the immunotherapy.

We understand that private insurers are following the CMS lead, and are reimbursing for Provenge.

Supply issues for DNDN

Dendreon says that, initially, demand for the drug will exceed supply as the company finishes building out its three manufacturing facilities in Los Angeles, Atlanta and New Jersey. For the drug launch, New Jersey facility will operate at 25% capacity, which will allow Dendreon to provide Provenge to about 2,000 patients in the next 12 months. All three facilities are expected to be fully operational by mid-2011, allowing sales of USD1.2 bn worth of the drug, according to the company.

We understand that DNDN is using the American Red Cross to perform the collection of cells for the Provenge treatment, and this has had supply issues. We would expect PRR to work through any kind of manufacturing issues the closer it gets to market.

What is the difference between PRR and DNDN in terms of manufacturing?

Compared to DNDN, we believe that PRR has a new, more automated process. PRR requires that the patient be apheresed once vs. the required three times as a part of the DNDN process. Developed in Germany, the manufacturing of PRR's required cells requires subcutaneous injection vs. DNDN's intravenous injection.

As a fast follower, we believe PRR's manufacturing technology has the potential is certainly no worse than Dendreon's (DNDN), and quite possibly is better.

DNDN's Neuvence – will this compete with C-Vac?

Potential competing products: Neuvence, (generic name: Lapuleucel-T [APC 8024]), is a therapeutic cancer vaccine at the clinical trial stage by Dendreon. It uses the immunotherapy platform approach first successfully demonstrated in Provenge. First Neuvence trials were performed on patients with metastatic breast, ovarian or colorectal cancer that expressed HER-2 (HER2/neu) and is now scheduled to be tested on bladder cancer patients. In particular, Lapuleucel-T is an investigational active immunotherapy product consisting of autologous peripheral blood mononuclear cells, including antigen presenting cells, which are cultured ex vivo with BA7072, a recombinant fusion antigen consisting of portions of the intracellular and extracellular regions of HER-2/neu linked to granulocyte-macrophage colony-stimulating factor. DNDN is planning a bladder cancer clinical trial using Neuvence to begin 2011. We will be watching to see if DNDN starts a clinical trial in ovarian cancer. We believe this is because bladder cancer is uniquely sensitive to immunotherapy, and hence is an easier target for therapy.

Nomura viewpoint

Given the development of the research in the field of immunotherapy over the past decade, we have increasing confidence in the role of immunotherapy in cancer.

We note that the equivalent results of a comparison of C-Vac and sipuleucel-T in their Phase II trials. Hence, there is potential for C-Vac will get to market.

Note that the sipuleucel-T Phase III trial had a relative reduction of 22% in the risk of death. We would be looking for this level of relative reduction in the risk of death in a Phase III trial. As a fast follower, we believe PRR's manufacturing technology has the potential and is certainly no worse than Dendron's (DNDN), and quite possibly is better.

Appendix: the regulatory approval process in the US

What is marketing authorisation?

To market a drug or biological product in the US, a prospective manufacturer must provide adequate information to the FDA demonstrating that the product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labelling for the product. This is known as a marketing authorisation. A marketing authorisation document generally includes the results of:

New drug application (ANDAs), abbreviated

New drug applications (NDAs), or

Biological license applications (BLAs)

PRR requires an NDA, as it is seeking approval of a drug. PRR's NDA submission will follow from the pre-NDA meeting with the FDA, and which PRR would have received guidance on the structure of its application from the FDA.

NDAs

The New Drug Application (NDA) is the vehicle in the US through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing. The goals of the NDA are to provide enough information to permit FDA reviewers to establish the following:

- Is the drug safe and effective in its proposed use(s) when used as directed, and do the benefits of the drug outweigh the risks?
- Is the drug's proposed labelling (package insert) appropriate, and what should it contain?
- Are the methods used in manufacturing (Good Manufacturing Practice, GMP) the drug and the controls used to maintain the drug's quality adequate to preserve the drug's identity, strength, quality, and purity?
- Comprehensive data to assess risk-benefit balance
- In general, randomized active and placebo-controlled trials required
- Phase IV: "Follow-up" studies of (dose-response), therapeutic use

Hence, the NDA will include evidence from clinical trials as well as evidence that the drug can be manufactured and marketed safely. The legal requirement for approval is "substantial" evidence of efficacy demonstrated through controlled clinical trials. Data for the submission must come from rigorous clinical trials.

The trials are typically conducted in three phases:

- **Phase 1:** The drug is tested in a few healthy volunteers to determine if it is acutely toxic.
- **Phase 2:** Various doses of the drug are tried to determine how much to give to patients.
- **Phase 3:** The drug is typically tested in double-blind, placebo controlled trials to demonstrate that it works. Sponsors typically confer with FDA prior to starting these

trials to determine what data is needed, since these trials often involve hundreds of patients and are very expensive.

- **Phase 4:** These are post-approval trials that are sometimes a condition attached by the FDA to the approval.

The legal requirements for safety and efficacy have been interpreted as requiring scientific evidence that the benefits of a drug outweigh the risks and that adequate instructions exist for use.

An NDA is reviewed by a multidisciplinary team of physicians, statisticians, chemists, pharmacologist/toxicologists, clinical pharmacologists, and microbiologists. The FDA has 6 months to take an action on a priority application and 10 months for a standard application. Most applications are either discussed with an FDA consultant or at a meeting of the Oncologic Drugs Advisory Committee (ODAC).

Common reasons for rejection of a NDA

This includes:

- Negative trials;
- Claims based on exploratory subgroup analysis;
- Non-inferiority (switch) but control arm not-established;
- A posteriori defined non-inferiority margins
- Marginal activity, safety issues;
- Lack of randomized control trial (RCT) – this is the most common reason for rejection; and
- No dramatic activity

An open-label trial or open trial is a type of clinical trial in which both the researchers and participants know which treatment is being administered. This contrasts with single blind and double blind experimental designs, where participants are not aware of what treatment they are receiving (researchers are also unaware in a double blind trial). Open-label trials may be appropriate for comparing two very similar treatments to determine which is most effective.

Although prospective definition of response criteria is critical in any clinical trial, independent confirmation of response by an expert review panel is perhaps more important in the open-label, nonrandomized studies that frequently form the basis of New Drug Applications.

Appendix A-1

Analyst Certification

I, David Stanton, hereby certify (1) that the views expressed in this Research report accurately reflect my personal views about any or all of the subject securities or issuers referred to in this Research report, (2) no part of my compensation was, is or will be directly or indirectly related to the specific recommendations or views expressed in this Research report and (3) no part of my compensation is tied to any specific investment banking transactions performed by Nomura Securities International, Inc., Nomura International plc or any other Nomura Group company.

Issuer Specific Regulatory Disclosures

Mentioned companies

Issuer name	Ticker	Price	Price date	Stock rating	Sector rating	Disclosures
Merck KGAA	MRK GR	EUR 67.54	31-Oct-2011	Buy	Bearish	
Prima Biomed Ltd	PRR AU	AUD 0.19	31-Oct-2011	Buy	Not rated	

Previous Rating

Issuer name	Previous Rating	Date of change
Merck KGAA	Not Rated	31-Mar-2009
Prima Biomed Ltd	Not rated	01-Nov-2011

Prima Biomed Ltd (PRR AU)

AUD 0.19 (31-Oct-2011) Buy (Sector rating: Not rated)

Chart Not Available

Valuation Methodology We ascribe a 62.4% risk-weighting for the C-Vac opportunity, as we believe PRR will begin a Phase III clinical trial by 4QCY11. Our risk-weighted valuation for PRR is A\$0.31 per share.

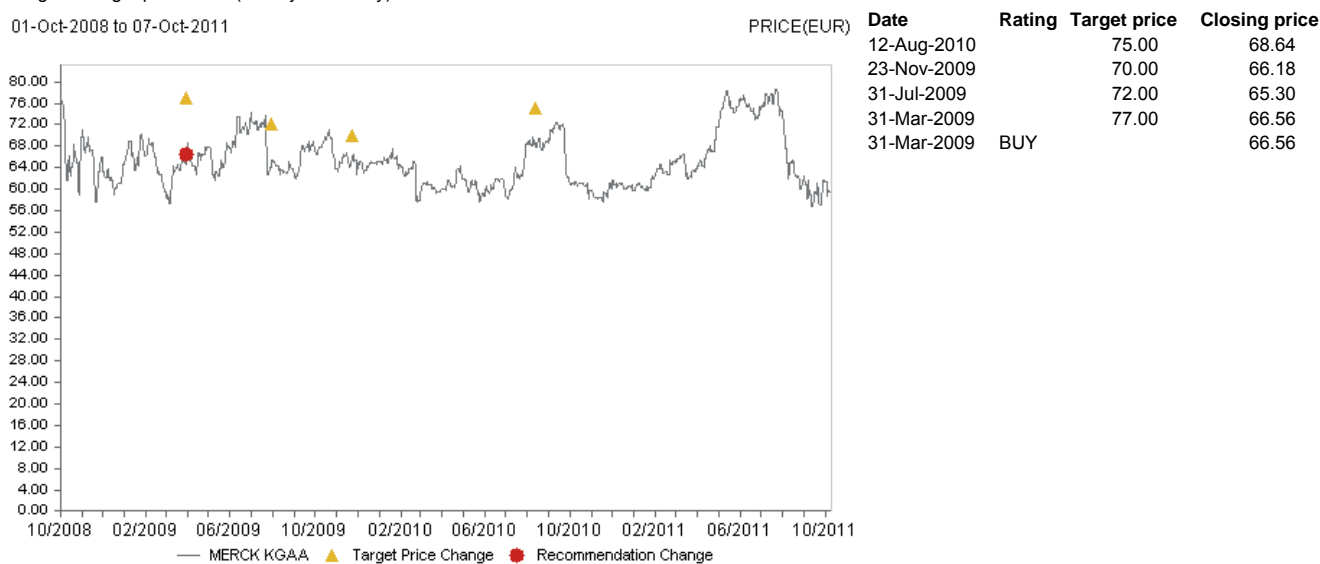
Risks that may impede the achievement of the target price There is still a good deal of uncertainty around PRR's viability in most of its prospective markets. Early clinical trials, although positive, give no real enough indication of a product's true viability and full foresight on future market conditions is difficult to obtain. Therefore we believe this is an investment opportunity for investors with a higher risk appetite.

Merck KGAA (MRK GR)

EUR 67.54 (31-Oct-2011) Buy (Sector rating: Bearish)

Rating and target price chart (three year history)

01-Oct-2008 to 07-Oct-2011



For explanation of ratings refer to the stock rating keys located after chart(s)

Valuation Methodology We value Merck KGaA against its European speciality pharma sector peers. A 40% discount (in line with historical trading levels for the stock) to the 2011 mid-cap sector multiple of 15.9x when applied to a '11E EPS (underlying core EPS of EUR 7.16) of EUR 7.37 gives a value per share of EUR 68. Our DCF with FCF projections till 2019 and WACC of 7.7% gives a value per share of EUR 68. Our target price stands at EUR 75. The relative index for these stocks is Dow Jones Euro STOXX® TM Pharmaceuticals.

Risks that may impede the achievement of the target price In addition to the typical pharma industry risks associated with potential product approval delays and product withdrawals, this company has substantial non-pharma cyclical operations.

Important Disclosures

Online availability of research and additional conflict-of-interest disclosures

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Explanation of Nomura's equity research rating system for Asian companies under coverage ex Japan published from 30 October 2008 and in Japan from 6 January 2009

STOCKS

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STOCKS

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Explanation of Nomura's equity research rating system for Asian companies under coverage ex Japan published prior to 30 October 2008

STOCKS

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A **'Strong buy'** recommendation indicates that upside is more than 20%. A **'Buy'** recommendation indicates that upside is between 10% and 20%. A **'Neutral'** recommendation indicates that upside or downside is less than 10%. A **'Reduce'** recommendation indicates that downside is between 10% and 20%. A **'Sell'** recommendation indicates that downside is more than 20%.

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