22 May 2013 | 52 pages

Drugs (Citi)
Europe | United Kingdom

Immunotherapy – The Beginning of the End for Cancer.

Transforming Cancer into Chronic Disease. Winners and Losers

- **Immunotherapies—$35bn potential/annum**, will likely become the treatment backbone in up to 60% of cancers over the next 10 years compared with <3% today. The current explosion in all ongoing approaches (including checkpoint agents, vaccines and cell therapy) to utilise the immune system to seek and destroy cancer cells marks a watershed, analogous to the impact of HIV drugs transforming life expectancy in HIV, in our view. Elucidation of biomarkers and a pro-science FDA should translate into rapid acceleration in development and approval. The revenue/patient should continue to increase given dramatic improvements in survival, multiple lines of therapy, and migration towards combined immunotherapy strategies. We prefer EU over US names. We have upgraded BMY to BUY, PT $55 and Roche to BUY, PT SFr300. Our favoured global names are BUY-rated BMY, Roche, Novartis and Sanofi.
- **Building an Immunotherapy basket**. We have constructed an immunotherapy basket for investors. Details about the basket and performance data can be found under the Bloomberg ticker CGRBIMMU. We see BMY and Roche as best positioned in this emergent area given their advanced checkpoint agents and developmental expertise in cancer. We are more optimistic over AZN's early checkpoint portfolio than GSK's later stage therapeutic vaccine program. While MRK has lambrolizumab (an anti-PD1) in phase I/II trial, we note reports of drug-related anorexia and the company's limited oncology experience. We remain upbeat over Novartis's cell therapy approach in treatment refractory patients. Other names in the basket include Amgen (blinatumomab), Incycte (IDO inhibitor)
- **Consensus is not reflecting the use of checkpoint agents, which should extend well beyond the initial indications, driving up to $24bn peak revenue**. We believe market forecasts currently neglect (i) the potential for anti-PD1/L1 antibodies outside the initial melanoma, renal and NSCLC (lung) indications; (ii) combination therapy with other agents will likely result in significant checkpoint agent efficacy in multiple solid and blood cancers; (iii) combination pricing – we expect the market to move quickly towards PD1/ PDL1 combinations with fellow immune-inhibitors such anti-LAG-3, anti-KIR (both BMY), and immune-stimulators such as anti-CD137 (BMY, PFE) and anti-OX40 (AZN); and we also think (iv) duration of therapy under-appreciated given both increased survival and retreatment rate
- **3x uplift to EVA/drug from accelerated time to market** assuming a two-year reduction in development time. The likely dramatic efficacy benefits of these agents within pre-selected population allow for smaller, shorter and less expensive clinical trials. Separately, the increasingly supportive FDA continues to look for novel development programs to accelerate time to market.

■ Industry Overview

Must

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Favoured Names and Profiles

Figure 1. Bristol Myer Squibb is now our favored Major name in the Global Pharmaceuticals

	Movement		Rating	Price Target	Investment Thesis	Cancer Immuno-therapy	"Shrink, Smarten, Spin"	Biologics	Vaccines	Diagnostics	Consumer Health	Emerging Markets	Generics	Animal Health
Most Favoured	↑↑	Bristol Myers-Squibb	Buy	$55.00	Pipeline, Dividend	✓✓✓	✓✓✓	✓✓✓				✓		
	↑↑	Roche	Buy	CHF 300.00	Innovation, pertuzumab	✓✓✓	✓✓	✓✓✓		✓✓✓		✓✓		
	↓	Novartis	Buy	CHF 83.00	Innovations vs Generics	✓✓	✓	✓	✓	✓	✓	✓	✓✓✓	✓
	↓	Sanofi	Buy	€101.00	Return to sustainable growth		✓✓✓	✓	✓✓✓		✓✓✓	✓✓✓	✓	✓✓✓
	↓	Pfizer	Buy	$31.00	Cost, WC De-equitisation		✓✓✓	✓✓	✓✓			✓✓	✓	✓✓✓
	↓	Bayer	Buy	€90.00	Xarelto, Emerging Markets		✓	✓✓		✓	✓✓✓	✓✓	✓	✓
	↓	GlaxoSmithKline	Buy	£18.10	Pharma 2.0 diversification	✓	✓✓✓	✓	✓✓✓		✓✓✓	✓✓		
	↓	Novo Nordisk	Buy	DKK 1150.00	Emerging market, diabetes		✓	✓✓✓				✓✓		
	↓	Allergan	Buy	$124.00	Sustainable growth, Innovation		✓✓	✓✓				✓✓		
	↓	Forest Labs	Buy	$44.00	Pipeline, Commercial launches		✓✓✓							
	↓	Shire	Buy	£22.50	Rare diseases innovation		✓✓	✓✓				✓		
	↓↓	Eli Lilly	Buy	$60.00	Pipeline base incl. Alimta, EM		✓✓✓	✓✓✓				✓		✓✓
	↓	Merck KGaA	Neutral	€120.00	Cost cutting, business development		✓	✓✓	✓	✓	✓	✓		
	↔	Merck & Co	Neutral	$44.00	Cost, WC reduction pipeline	✓		✓✓	✓✓✓		✓	✓		✓✓✓
Least Favoured	↔	AstraZeneca	Neutral	£30.00	Shrink research. De-equitisation growth drivers	✓	✓✓	✓	✓			✓		

Shaded – US Companies Source: Citi Research

Transforming Cancer into Chronic Disease

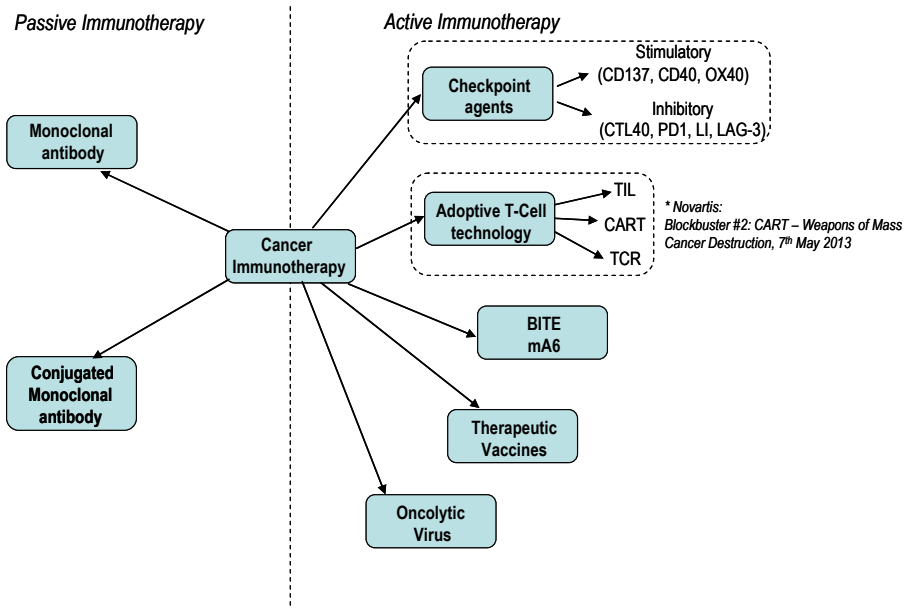
What is cancer immunotherapy? Immunotherapeutic approaches leverage the patient's immune system to eliminate or slow the growth and spread of cancerous cells. The use of immunotherapy dates back to 1850 when German physicians noted that occasionally tumours would shrink if the tumour became infected. Older biologic agents such as interferon alpha2b and Proleukin (IL2) were used with some effect in the 1990's but had limited impact given high toxicity and limited patient responsiveness in only select tumour types. New advances in tumour biology are enabling the development of newer potent T cell mediated therapies that prevent the tumour from evading immune detection with manageable safety profile. Experimental T-cell immunotherapy comprises multiple modalities. These include checkpoint inhibitors (CTLA4 mediated like BMY's Yervoy, PD1/ PD-L1 mediated like BMY's nivolumab, CD137 etc), therapeutic vaccines such as GSK's MAGE-A3, Amgen's T-Vec and Vical's Allovectin, bispecific antibody-based approaches such as Amgen's blinatumomab, small molecules such as Incyte's IDO inhibitor (INC'360) and more recently cell-based therapies such as Dendreon's Provenge and Novartis CTL-019/CART-19. We estimate the market for immunotherapeutic approaches in cancer treatment will likely exceed $35bn by 2023, driven by novel agents, combination therapy, longer treatment times and the emergence of predictive biomarkers. Bristol Myers, Roche and Novartis look well positioned in this important emergent market.

Cancer is the developed world's second most common cause of death. Lifetime cancer risk in the Western world is 1/2 and a cause of death in 1/4 of individuals. The economic cost of cancer in the US was estimated in 2008 at $200bn per annum, including $80bn for total healthcare costs. Rapidly accelerating advances in immunotherapy make it a potential tool to transform a significant percentage of cancers into something akin to a chronic disease. We draw parallels with the much smaller HIV population where HIV therapies have transformed life expectancies, with significant medical and economic implications.

Immunotherapy will likely form the backbone of c.60% of all cancer treatment in 10 years compared with <3% today

We believe that, in 10 years, immunotherapy will likely form the backbone of 60% of all cancer management regimes in the developed world given likely paradigm shifting changes in OS improvements in responsive patients. This represents a potential revenue opportunity for the industry in excess of $35bn by 2023, exceeding the peak market value of historical mega-blockbuster classes, such as the statins for elevated cholesterol. This report outlines our view of the likely evolution of the immune-stimulatory approaches for cancer management over the next 5-10 years, identifying timelines and winners and losers from among the industry. We anticipate that the emergence of these new molecules will have an equal, or even greater, impact on the management of many cancers as Herceptin and Rituxan have had on breast and B cell malignancies respectively.

Figure 2. Expanding treatment modalities of immunotherapy.

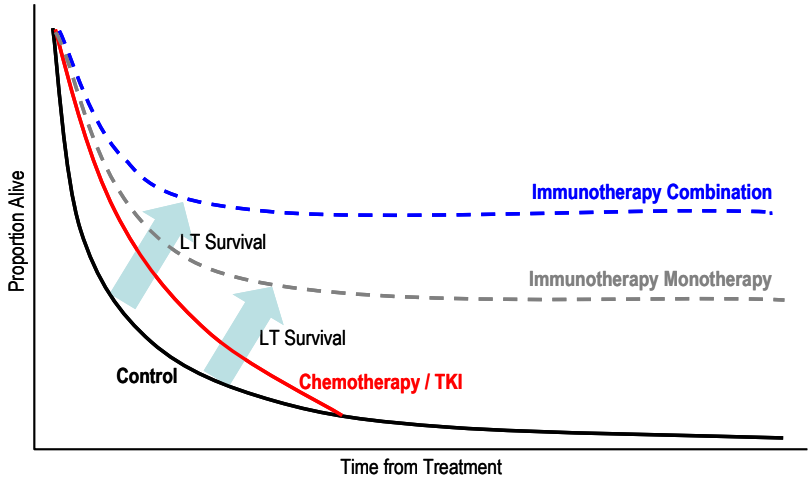


Source: Citi Research. *Novartis CART note can be accessed here* http://goo.gl/avYfS

Immunotherapeutic agents in cancer are associated with a much more durable response than conventional chemotherapy/ TKI's

While conventional chemotherapy or tyrosine kinase inhibitors have a powerful initial effect on tumour shrinkage (the so called "response rate"), the durability of these responses are typically very short, after which the tumour begins to grow again and starts to spread (metastasize). In contrast, the durability of responses with immunotherapy can last a decade, due to the induction of an ongoing immunological memory, targeting cancer cells for an indeterminate length of time.

Figure 3. Immunotherapy responders can experience a dramatic impact on survival compared with conventional chemotherapy due to durability of response.



Source: Citi Research

Commercial potential highly underappreciated; we think potential likely 2-3x higher driven by:

Commercial potential grossly underappreciated. We believe that the published estimates of potential sales of the Checkpoint Agents class at $7bn are highly conservative.

We anticipate that the market for checkpoint agents alone could ultimately reach as high as $24bn, driven by:

i) High demand from patients

- High adoption rates in Western countries, given immunotherapies have a largely well-tolerated adverse event profile compared with conventional chemotherapy (excluding cell therapy);

ii) Rising duration of therapy

- Immunotherapy treatment months/patient to likely materially expand due to (a) improved PFS associated with immunotherapy; (b) multiple lines of therapy during a patient's disease; (c) maintenance usage;

iii) Rising price/patient through adoption of combination therapy

- Unit price of therapy set to increase associated with migration to checkpoint combination therapy;

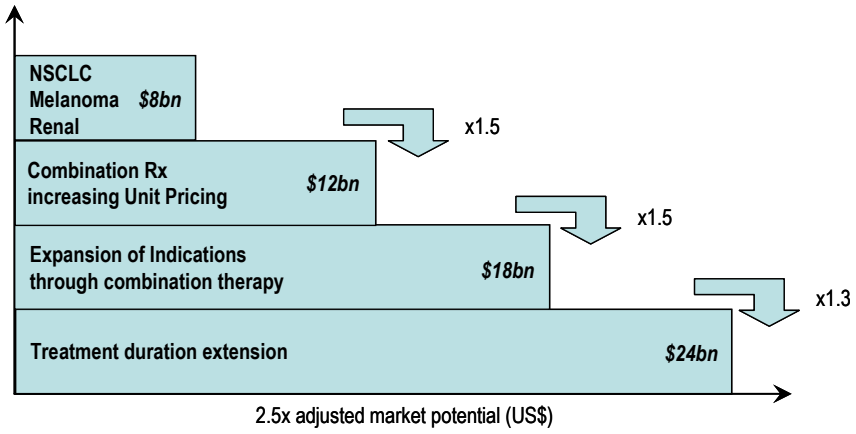
iv) Potential for use in multiple lines of therapy

- Likely use of repeat immunotherapy based approach in patients who lose their partial response, given well tolerated adverse event profile and mechanistic rationale;

v) Expansion of use in other cancers beyond the initial indications of lung, skin and renal cancers

- Combination strategies with chemo/radio/MAb/cryotherapy or other checkpoint inhibitors will likely expand the potential indications for checkpoint agents well beyond NSCLC, melanoma and renal cancer.

Figure 4. Checkpoint agents have market potential in excess of $20bn by 2021

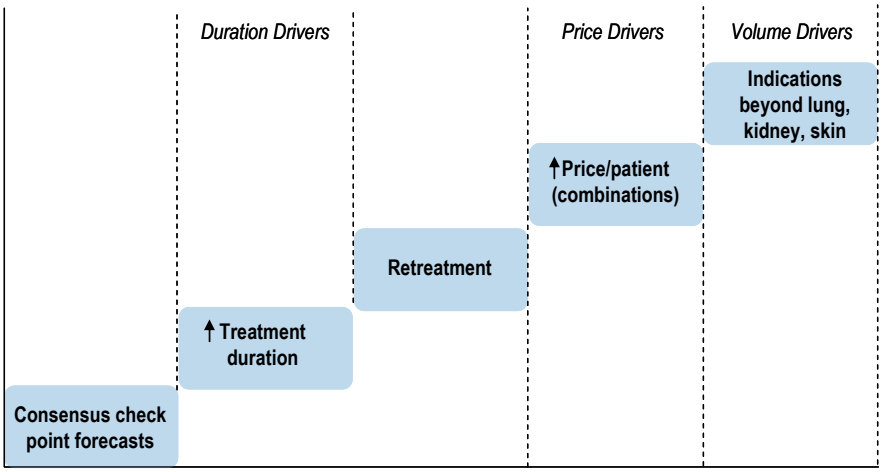


Source: Citi Research

Cancers not normally immunotherapy-sensitive can be induced to become highly sensitive to immunotherapies, rapidly expanding the addressable market

The market is not reflecting the likely breadth of oncology indications addressable with immunotherapeutic approaches. Investor awareness of immunotherapy is largely limited to melanoma and renal cancer, and more recently NSCLC given the recent PD1 data. We believe that, ultimately, immunotherapy will form the backbone of treatment for up to 60% of metastatic disease and perhaps 30% of adjuvant therapy. Tumours traditionally thought of as non-immunogenic can likely become immunogenic and respond to immunotherapy through co-administration of pro-immunogenic therapies designed to increase antigen release from the cancer cell, effectively mimicking the actions of a vaccine. Potential priming agents for immunotherapy include chemotherapy (traditional or TKI), monoclonal antibodies such as Erbitux, Herceptin and Rituxan, radiotherapy and even cryotherapy.

Figure 5. Market potential for checkpoint inhibitors remains underappreciated



Source: Citi Research

Figure 6. Core Earnings – Bristol & Roche 27% and 21% respectively above consensus

BMY			2013	2014	2015	2016	2017	2018	2019	2020
Sales	Citi	new	16,522	17,676	18,211	19,988	22,661	25,004	27,962	30,399
		old	16,505	18,174	18,111	18,842	20,675	22,135	23,403	24,915
		Δ	***0%***	***-3%***	***1%***	***6%***	***10%***	***13%***	***19%***	***22%***
	Cons		16,450	17,737	17,855	18,804	20,709			
		% Citi vs Cons	*0%*	*0%*	*2%*	*6%*	*9%*			
non-GAAP EBIT	Citi	new	3,292	4,264	4,014	4,646	6,483	7,762	9,657	11,345
		old	3,190	4,099	4,075	4,145	5,065	5,866	6,202	6,727
		Δ	***3%***	***4%***	***-1%***	***12%***	***28%***	***32%***	***56%***	***69%***
	Cons		3,370	4,043	3,686	3,856	4,782			
		% Citi vs Cons	*-2%*	*5%*	*9%*	*20%*	*36%*			
non-GAAP EPS	Citi	new	1.83	2.29	2.13	2.43	3.35	3.99	4.96	5.84
		old	1.79	2.09	2.08	2.11	2.56	2.95	3.12	3.39
		Δ	***2%***	***10%***	***2%***	***16%***	***31%***	***35%***	***59%***	***72%***
	Cons		1.82	2.16	2.07	2.14	2.63			
		% Citi vs Cons	*0%*	*6%*	*3%*	*14%*	*27%*			

Roche			2013	2014	2015	2016	2017	2018	2019	2020
Sales	Citi	new	47,196	50,322	52,288	55,039	59,529	63,938	67,313	70,956
		old	47,028	48,023	48,925	50,142	52,429	55,024	56,136	56,063
		Δ	***0%***	***5%***	***7%***	***10%***	***14%***	***16%***	***20%***	***27%***
	Cons		47,832	49,712	51,679	53,443	54,870			
		% Citi vs Cons	*-1%*	*1%*	*1%*	*3%*	*8%*			
Core EBIT	Citi	new	18,315	19,888	20,923	22,505	25,388	28,118	30,226	32,565
		old	18,235	18,767	19,000	19,350	20,238	21,624	20,858	20,433
		Δ	***0%***	***6%***	***10%***	***16%***	***25%***	***30%***	***45%***	***59%***
	Cons		17,405	18,504	19,617	20,537	21,587			
		% Citi vs Cons	*5%*	*7%*	*7%*	*10%*	*18%*			
Core EPS	Citi	new	15.48	17.44	18.76	20.59	23.27	25.83	27.82	30.01
		old	15.40	16.38	16.94	17.62	18.44	19.75	19.05	18.67
		Δ	***1%***	***6%***	***11%***	***17%***	***26%***	***31%***	***46%***	***61%***
	Cons		14.87	15.98	17.01	18.19	19.21			
		% Citi vs Cons	*4%*	*9%*	*10%*	*13%*	*21%*			

Source: Citi Research, consensus from Factset

Clinical development time shrinking from 7 to 4 years driven by high magnitude of efficacy and an accommodating FDA

Rapid time to US approval. The newly empowered FDA is clearly indicating its intent to approve novel immunotherapies on the back of significant differences in overall response rate compared with standard of care coupled with interim analysis of PFS. We anticipate approval of BMY nivolumab on interim analysis in mid 2014 and Roche filing its anti-PDL1 approximately 12 months later. Novartis will likely file its CART-19 for CD19 blood cancers in late 2014.

EMA appears behind FDA, but likely to follow suit eventually

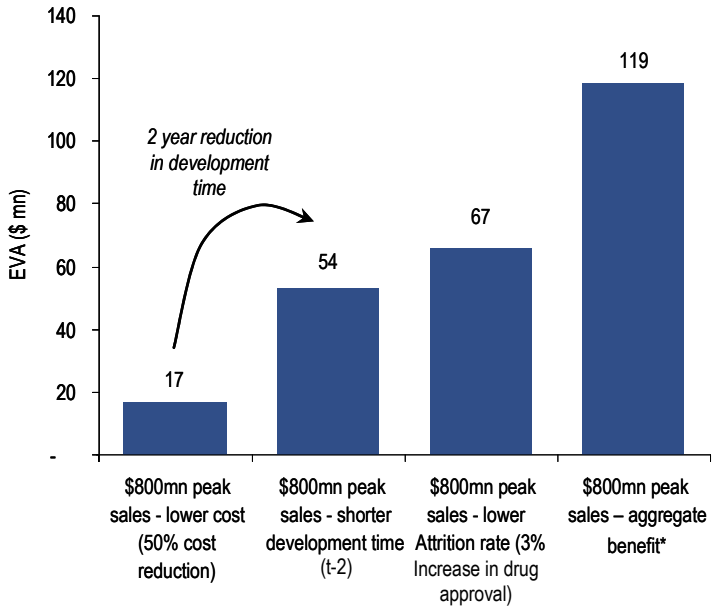
The EMA currently continues to request demonstrated improvements in overall survival compared with the standard of care. However, we believe that, ultimately, the EMA will adopt the FDA's somewhat more realistic regulatory hurdle, although it may slow EU approval in the interim.

Consequently, we anticipate that the development time for a novel immunotherapy from late pre-clinical to approval for a first-line metastatic setting could be 5 years and as little as 3 years in the end stage setting (such as autologous T cell transfers) in the US.

EVA/drug set to increase 3x given faster time to market, lower development cost

…with a dramatic positive impact on ROIC. The characteristics of immunotherapeutic drug development will likely translate into a materially higher ROIC than other oncology agents driven by (i) rapid development time (ii) lower attrition rate and (iii) small registration trials. The willingness of the FDA to accelerate the development of breakthrough drugs for unmet medical disease through greater use of the accelerated approval pathway, intermediate clinical endpoints or new 'breakthrough' pathways is clearly evident. We note that both MRK and Roche have elected to move direct from phase I to phase III trial programs substantially reducing the time to market. Although a lesser factor than time-to-market, the dramatic efficacy of immunotherapy in selected patients allows for smaller registration trials than traditional chemotherapy. We estimate that a 500-700 patient anti-PD1/PDL1 phase III outcome trial, powered to show a 30% risk reduction in mortality would cost an estimated $100-140m.

Figure 7. Reducing time to market by 2 years increases risk-adjusted EVA/Drug by 3x



*lower cost (50% cost reduction) + lower attrition rate (3% increase in drug approval) + shorter development time (t-2)

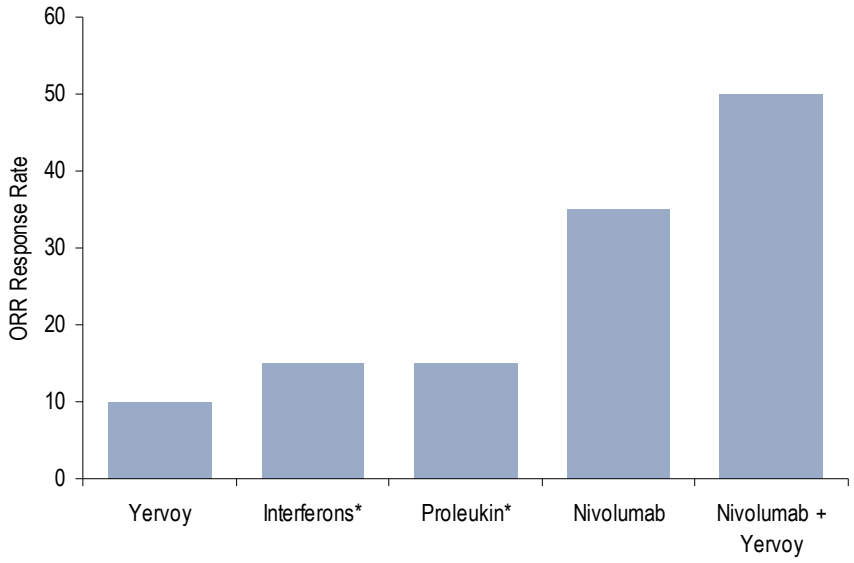
Source: Citi Research

Unlike traditional chemotherapy, ultimately the majority of patients will likely respond to immunotherapy combinations

Percentage of responders is set to rise as high as 60%+ in selected populations. We anticipate that response rates with immunotherapy will continue to rise through three mechanisms:

- *Checkpoint biomarkers accelerate clinical development and magnitude of response*. Enrichment strategies with marker positive patients should require small sample sizes and more rapid completion. We describe the positives and negatives of biomarker-based selection for PD1 trials in the following sections.
- *The evolution of combination immuno-modulatory approaches to maximise outcomes* and overcome the resistance mechanisms of most tumours to a single immuno-modulatory approach. Potential combinations include checkpoint agents combined with chemotherapy, tyrosine kinase inhibitors, radiotherapy, and therapeutic vaccines/ monoclonal antibodies/cryotherapy, as well as checkpoint/checkpoint combinations
- *The development of more potential immune-stimulatory approaches both within and outside checkpoint inhibitors*. We highlight immune-inhibitory agents LAG-3 and anti-KIR and immune-stimulatory agents anti-CD137 (1-4BB) and anti-OX40.

Figure 8. Anti-PD1/ PDL1 based therapies have materially higher response rates and greater tolerability than older agents Proleukin and Interferon.



Source: Citi Research, Company data

Immunotherapy applications extend to viral infections and autoimmune disease

Potential utility beyond oncology. The potential to selectively influence the T-cell mediated immune system may have important applications in anti-viral therapy, in particular for HPV and Herpes Simplex. In combination with current inhibitors, PD-1 and other checkpoint antagonists offer the potential to attain functional cure through eradication of viral load. In addition, immunotherapies have the potential for the treatment of autoimmune diseases by inducing self tolerance through down regulating the innate immune system. Potential indications include lupus, RA and psoriasis.

A full glossary addressing most of the commonly used medical terms is to be found at the end of this report

How do I invest in Immunotherapy?

Citi's proprietary Global Immunotherapy Basket: Bloomberg ticker CGRBIMMU.

We advocate that a carefully designed basket of equities reflecting key participants in emergent immunotherapies is likely the optimal way to invest, given the relative paucity of late stage clinical data. We would weigh the basket according to potential undiscounted upside within each immunotherapy name compared with the current market price and intrinsic value. Our sample basket is shown below in Figure 9.

BMY and Roche set to dominate the class of checkpoint agents. Merck is disadvantaged by its lack of oncology experience and breadth of assets

BMY and Roche are Likely Winners in Checkpoint Inhibitors Class. We anticipate drugs working on the PD1/PDL1 axis to form the backbone of treatment in a significant percent of cancers beyond the existing melanoma, renal and NSCLC indications. BMY looks to have a robust competitive position from multiple angles. It has a plethora of novel and potent checkpoint inhibitors in development (anti-CD137, anti-KIR to name but two), it has the most advanced anti-PD1 (nivolumab) in phase III development for NSCLC (non small cell lung cancer), renal cancer and malignant melanoma and it is the only pharmaceutical company with a potent CTLA4 checkpoint inhibitor already on the market (Yervoy). Our discussions with researchers have highlighted BMY's strong academic relationships in optimising their development programs for their gamut of compounds. Roche anti-PD-L1 (MPDL3280A) is c.2 years behind BMY in development but is likely to demonstrate a lower rate of pneumonitis (inflammation of the lungs). We anticipate phase II at ASCO 2013. While Roche has no other late-stage checkpoint inhibitors, it has an immune-conjugate platform and leading monoclonal antibody design expertise, which facilitates the development of many PD-1 based combination therapies. Roche's much larger R&D expense allows it to accelerate development compared with BMY, which is likely constrained by its much lower per annum R&D expense.

Merck has significant basic science research experience backing its anti-PD1. However, it is constrained by the absence of other immunomodulatory approaches within its pipeline compared with peers and suffers from a relative lack of oncology expertise compared with Roche, BMY and AZN. We note that MRK is moving rather more conservatively than its peers in its anti-PD1 development program.

AstraZeneca has an interesting, if early, immuno-oncology portfolio

AstraZeneca has an early but broad pipeline of immuno-therapies. Unlike Merck, it has had a high historic success rate with oncology drugs (Tamoxifen, Arimidex, Faslodex, Femara, Iressa etc). AZN in-licensed Pfizer's tremelimumab in 2011. Unlike BMY's Yervoy, tremelimumab failed to demonstrate a significant OS benefit, despite a similar mechanism of action and a similar ORR. The relative potency of tremelimumab vs. Yervoy is unclear. BMY claim pre-clinical and clinical data demonstrating inferior efficacy while AZN argues that poor trial design, dosing and cross over is responsible for its failure to demonstrate a survival benefit. AZN has indicated that it intends to explore tremelimumab in combination with PD1 and other immune-stimulatory molecules through a phase III program set to be initiated in 2014

Figure 9. Citi Immunotherapy Basket (CGRBIMMU)

Company	Immunotherapy	Treatment modality	Potential approval	Revenue potential
Bristol Myers Squibb	Yervoy, nivolumab, others	Checkpoint agent	Yervoy approved, others 2015+	$7bn
Roche	MPDL3280A	Checkpoint agent	2016	$7bn
Merck	lambrolizumab	Checkpoint agent	2017	$3bn
AstraZeneca	tremelimumab, anti-PD1, anti-OX40	Checkpoint agent	2018	$4bn
Glaxosmithkline	MAGE-A3 vaccine, anti-PD1	Therapeutic vaccine, Checkpoint agent	2015 for CART, 2018 for PD1	$3bn
Novartis	CART-19	Adoptive T cell therapy	2015	$3bn+
Amgen	blinatumomab, Tvec	Bi-specific antibody, therapeutic vaccine	2017	$2bn+
Vical	Allovectin	Gene therapy	2014	$1bn
Incyte	IDO'360	small molecule IDO inhibitor	2017	$2bn+

Source: Citi Research

Note: Details about the basket and performance data can be found under the Bloomberg ticker CGRBIMMU

Novartis, Amgen, Pfizer and Roche set to benefit from CD19+ve blood cancers

Novartis, Amgen, Pfizer and Roche set to benefit from CD19+ve blood cancers. Mortality rates will likely continue to decline given the improvements associated with Rituxan. The uniquely high expression of CD19 on cancer cells in these indications makes this an ideal addressable target for immunotherapy-based approaches. We have previously described Roche's GA101 and conjugated monoclonal anti-CD22. Roche's franchise faces competition from Amgen's bi-specific antibody for CD19 and CD3 (blinatumomab) that could become an important backbone for many CD19 malignancies. We note the recent encouraging 72% complete response rate shown in treatment refractory ALL.

We recently highlighted the commercial potential of Novartis's adoptive T cell transfer cell therapy with CART-19/CTL-19 in our recent in-depth report. CART-19 offers high potential in refractory end-stage patients. We anticipate the FDA to award breakthrough status with approval as early as 2016. However, we note that the bespoke administration and high incidence of cytokine storm may limit usage to end-stage patients with B cell malignancies. We anticipate sales of >$3bn by 2021.

Therapeutic vaccines remain promising but low expectations for GSK's MAGE-A3

Therapeutic vaccines remain promising but low expectations for GSK's MAGE-A3. While we remain upbeat longer-term that the right combination of adjuvant, vaccine, antigen, tumour and immune-modulator will ultimately translate into a clinical benefit, we now doubt that either of GSK's ongoing adaptive phase III programs in NSCLC and melanoma will translate into clinical success given our concern over the immunogenicity of the MAGE-A3 self antigen used in both programs. The recurrence of MAGE-A3 expressing tumours in vaccinated patients clearly casts some doubt over the T-cell response elicited by the vaccine. We believe that efficacy will require co-administration of checkpoint inhibitors, superior neo-antigens or even more potent adjuvants. Our model anticipates risk-adjusted sales of £216m for GSK in these two indications.

On a positive note, we are encouraged by the positive subgroup analysis from the recently announced failed phase III start trial with Stimuvax in NSCLC. There was a statistically significant (p=0.016) 22% reduction in the *post hoc* subgroup analysis of NSCLC patients treated with Stimuvax who had received initial concurrent chemo-radiotherapy compared to patients in the control arm. Although Merck will likely not be able to secure approval on this data, the positive signal demonstrates the potential importance of concurrent immuno/traditional therapies in increasing immunogenicity, likely through a broader activation of the immune system (presumably through epitope spreading, see page 19).

Seperately, Amgen recently announced top-line results from a Phase III trial of an anti-cancer virus as a treatment for metastatic melanoma, showing that talimogene laherparepvec (T-Vec) met the primary goal for shrinking tumours in patients with late stages of the disease.

IDO inhibitors look promising as potential combination agents with chemo and immunotherapeutic approaches

IDO inhibitors look promising as potential combination agents with chemo and immunotherapeutic approaches. The combination of IDO inhibitors could reprogram a immuno suppressive Treg immune cells into a non-suppressive T helper cell and thus bolster anti-tumour efficacy. Incyte has the highest potential IDO inhibitor (INCB'360) in phase II development ovarian, melanoma and myelodysplastic syndromes scheduled to report out in 2014/2015, while New Link Genetics has an ongoing 120 patient trial in metastatic breast cancer, scheduled to report in 2015.

Roche's Avastin, LLY's Alimta and CML agents Tasigna, Sprycel may experience revenue decline. Hospital revenue may be negatively impacted through lower radiotherapy usage and fewer hospital stays

Who loses? In terms of material revenue drivers, Roche has potentially the most to lose. Roche's >SFr 6bn/annum Avastin franchise looks at risk from the use of anti-PD1 and other immune-stimulatory agents in NSCLC. However, we note that there is a mechanistic rationale for combined use of an anti-PDL1 agent with Avastin, which if successful, may limit competitive risk (see Figure 11). In CD-19 expressing blood cancers, Roche faces increased competitive risk to both its Rituxan franchise as well as its newer NHL/CLL modalities such as GA101 and anti-CD22 (RG7593).

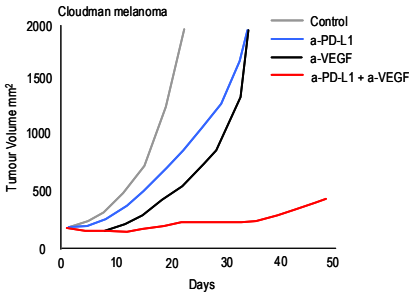
LLY's Alimta estimates in NSCLC may be at risk depending on the outcome of the ongoing phase III trials with BMY's nivolumab. Celgene's Abraxane may also face intensified competitive pressures within the NSCLC indication

Looking further out, we see potential risk to currently used TKIs in CML (Novartis' Glivec/Tasigna, BMY's Sprycel and Ariad's Iclusig) given the potential to achieve high rates of functional cure with PD1 agents combined with short duration TKIs. Longer-term competitive risk outside these indications depends on the clinical data from the emergent combinations of immuno-modulatory agents in indications, such as breast and colorectal cancer, which generate significant revenue for currently approved drugs such as Avastin.

Potential for hospital radiation oncology revenues to be negatively impacted

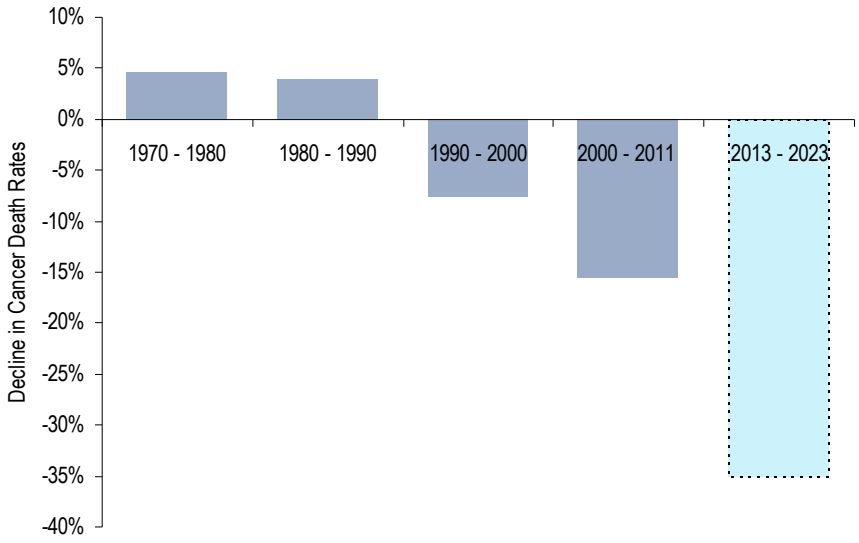
Dependent on the breadth of treatment effect, we anticipate that immunotherapy usage could negatively impact fee-for-service hospital revenues through reducing hospital readmission and lowering utilisation of palliative radiotherapy, a key earnings contributor. We estimate that hospitals derived an estimated 5-10% of their earnings from radiation oncology services. We estimate the ultimate impact could be greater, driven by lower hospitalisations for end-stage cancer patients on account of lower/delayed mortality.

Figure 11. . Avastin shows synergy with anti-PD1 in animal models



Source: Citi Research, Company data

Figure 10. Immunotherapy could accelerate the decline in cancer mortality rates, thereby negatively impacting hospitals that continue to operate under a fee for service model



Source: CDC, Citi Research

What are Immune Checkpoint Agents?

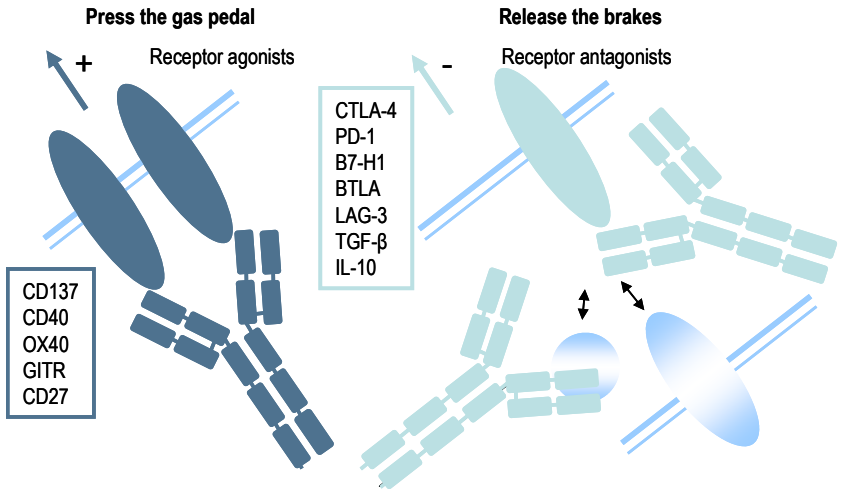
Checkpoint agents elicit a stronger anti-tumour response by removing tumour camouflage or potentiating the immune system

Checkpoint agents elicit a stronger anti-tumour response by removing tumour camouflage or potentiating the immune system. Tumour cells are cells that grow, divide and spread without proper regulatory control. Many kinds of tumour cells display unusual antigens that are either inappropriate for the cell type and/or its environment, or are only normally present during the organisms' development (e.g. fetal antigens). Tumour-specific antigens include MAGE-A3, MUC-1, Erb-2, mesothelin etc. The ability of tumour cells that bear these antigens to survive the body's immune system reflects the ability of the tumour cell to camouflage itself from the immune system by inducing immune tolerance. Immunotherapy attempts to remove the induced immune tolerance through two key mechanisms, often referred to as the accelerator and the brake (see Figure 12).

Checkpoint blockers like Yervoy and the PD1/PD-L1 mediated agents release the brake on the immune system

Unlike other immunotherapies or cancer vaccines that work by strengthening the immune system or training it to attack tumour cells, checkpoint inhibitors work to defeat a cancer resistance mechanism that causes immune cells to see tumour cells as *"self"*. Once this veil or "brake" is lifted, the immune response may be enough to defeat the cancer cells on its own, but a wide ranging array of therapeutic combinations is being tested. PD-1 or programmed death is a checkpoint molecule in the same family as CTLA4, the molecule targeted by Yervoy. T cells are immune cells that are ordinarily activated in response to cancer cells in order to seek and destroy them. They have a regulator switch in the form of PD-1 on their surface to stop their destructive activity once the target cells are gone, a failsafe device to stop them from destroying healthy tissue — hence, the origin of the term immune checkpoint. However the tumour cells have adapted by producing the ligand PD-L1 and PD-L2 on the surface. This naturally produced ligand binds PD-1 and trips the shutdown switch. The objective of checkpoint directed immunotherapies is to come between the receptor and the ligand, turning the switch back on and freeing the T cells to attack cancer.

Figure 12. Immunostimulatory mAbs can act moderate the interaction between the immune system and the tumour cell to enhances immunoreactivity by "removing a brake" or "pressing the gas pedal"



Schematic representation of the concept of immunostimulatory mAbs Concept and examples of agonist and antagonist mAbs directed toward activatory or inhibitory receptors of immune system cells. Green means activatory receptor and agonist antibody, whereas red means inhibitory receptor and antagonist antibody. Examples of immunostimulatory mAbs in advanced development of each kind of antibodies are framed in the corresponding color.

Source: I. Melero, 2013 American Association for Cancer Research, Citi Research

The ubiquitous nature of Yervoy's target increases the prevalence of immune related adverse events compared with PD1 mediated therapies

Yervoy's target, CTLA4 is engaged early in the process of T cell activation. Its ligand is expressed on antigen presenting cells, such as the immune systems dendritic cells which are found throughout the body giving Yervoy a more global effect on immune activity. In contrast, PD-1 is largely expressed only on T cells that have migrated into peripheral tissues, with the ligands are expressed there. The comparative toxicity of anti-PD1 compared with Yervoy is nicely demonstrated in knockout mice models born lacking either Yervoy receptors or PD1 receptors. CTLA4 knockout mice die within four weeks from profound immune-related adverse events. In contrast, PD1 knockout mice have relatively normal life expectancy.

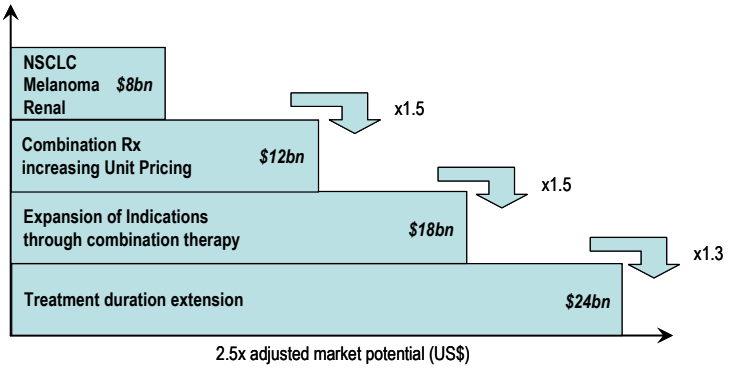
Checkpoint agonists or stimulators potentiate T cell activity against tumour cells.

Separate from the checkpoint inhibitors ("the brakes"), there is a second class of checkpoint mediated molecules in development called checkpoint agonists or stimulators. These agents, listed in Figure 21, are akin to effectively depressing the 'accelerator' or gas pedal on the T cell. Binding with the natural ligand or therapeutic antibody is potentially a more powerful, broader immune response. There is also evidence that checkpoint agonists are powerful agents in inducing T cell memory to tumor antigens improving immuno-surveillance and potentially reducing the risk of recurrence.

Our view: Consensus underestimates Checkpoint potential due to combination use

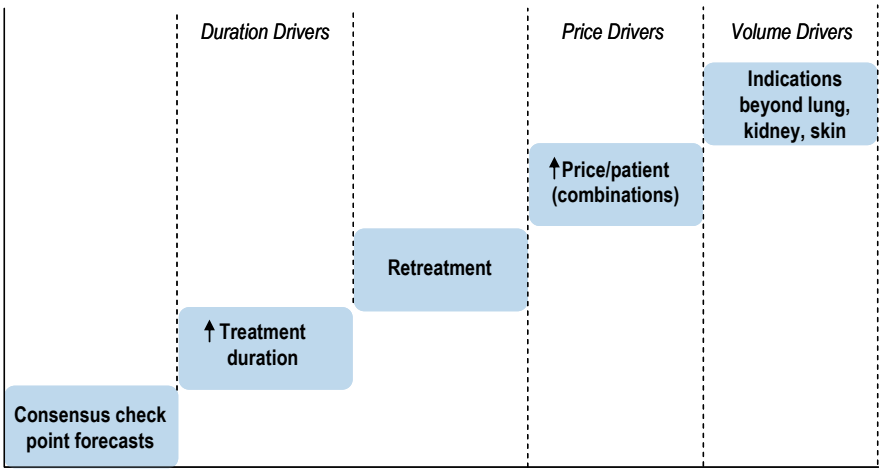
We think the market dramatically underestimating checkpoint agents potential – 5 key drivers of value.

Figure 13. Checkpoint agents have market potential in excess of $20bn by 2021



Source: Citi Research

Figure 14. Where consensus underestimates market for checkpoint inhibitors



Source: Citi Research

Efficacy and patient demand should drive market penetration for immunotherapy

We believe that the published estimates of the sales potential of the Checkpoint Agents class at c.$7bn is highly conservative. We anticipate that the market for checkpoint agents alone could ultimately exceed $20bn driven by:

1. *Indication expansion.* Combination strategies with chemo/radio/monoclonal antibodies/vaccines/cryotherapy or other checkpoint inhibitors will likely expand the potential indications for checkpoint agents well beyond NSCLC, melanoma and renal cancer through epitope spreading (pages 19). Combination treatments with the aforementioned modalities can elicit PD1 expressions (likely through IFN gamma production) and therefore convert a tumour to an anti-PD1/anti-PDL1 responder. Potential combinations for PD1-based therapy range from concomitant cryotherapy in adjuvant breast cancer, radiotherapy in NSCLC, and concomitant chemotherapy with TKI in CML. The magnitude of this call option is reflected in Figure 13.

2. *Market penetration*. Unlike 1st generation immunotherapies, we anticipate high adoption rates in Western countries given a largely well-tolerated adverse event profile compared with conventional chemotherapies (excluding cell therapy). Third-generation immunotherapies such as anti-PD1 have significantly fewer adverse events compared with IL2, IFN and more recently Yervoy. Additionally, advances in scheduling and early detection of immune related adverse events is set to material reduce the rate of grade 3 and 4 adverse events.

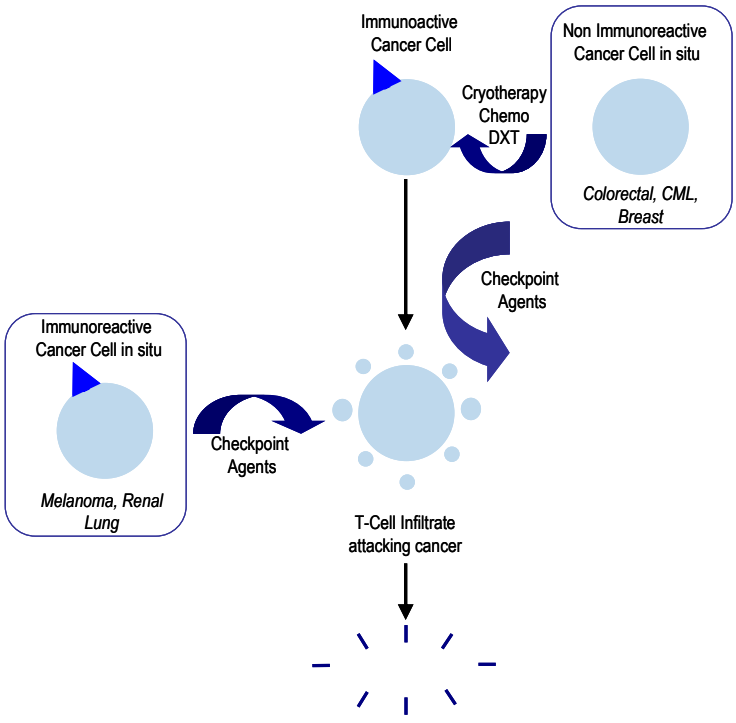
Months/ patients for immunotherapy will expand. Multiple lines of treatment of PD1 based therapy likely as patients progress

3. *Months/patient (duration) of immunotherapy will likely materially expand* given the anticipated improvements in progression-free survival time when immunotherapy is used as part of a combination regimen. The ongoing phase III trials are based around a 24-month duration of treatment. Increasing response rates due to biomarkers, combined with utilisation of combination therapies will likely result in the majority of patients receiving 24 months of treatment. We also anticipate that checkpoint agents will be used in multiple lines of therapy, likely as part of different combination regimens. Maintenance and adjuvant therapy are two additional drivers of increased treatment duration.

The unit price of therapy is set to increase driven by combination treatment

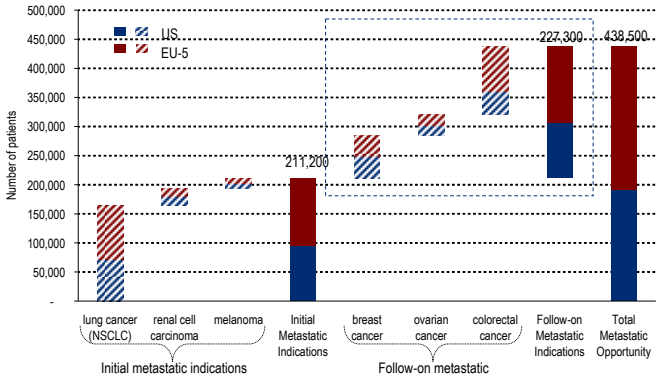
4. *The unit price of therapy is set to increase* associated with migration to checkpoint combination therapy. We have assumed a price per month for anti-PD1/PDL1 of $110,000 in the US in line with Yervoy and $80,000 in ROW. Similar to Perjeta, we anticipate that US will allow additional sales of $6-8bn for a second immuno-modulator to be used in combination with PD-1. This translates into a maximal unit price of $15-20,000/ month for combination therapy. We discuss an array of fourth generation co-immunostimulatory and coimmuno-inhibitory molecules in development. These include anti-LAG2, anti-KIR (both inhibitory) and anti-CD137 and anti-OX40 (both stimulatory).

Figure 15. PDL1 expression can be induced through combination with conventional chemotherapy/ DXT/ monoclonal antibodies or small molecule therapy.



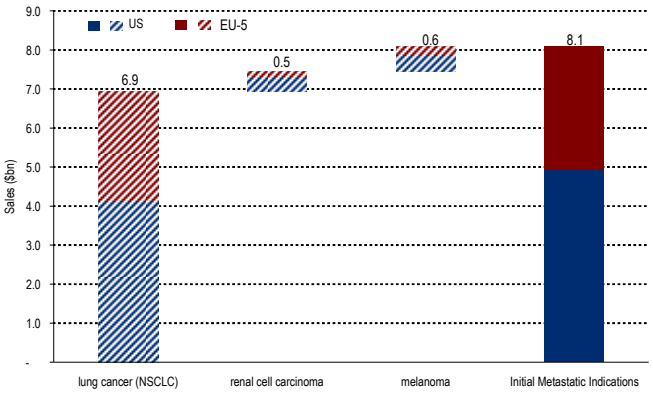
Source: Citi Research

Figure 16. Total number of patients that could potentially be treated by checkpoint agents



Source: Citi Research, Company Data. *Note: This is the total number of first-line drug treated patients across various indications regardless of PD-1 expression. PD-1 expression varies by indication.*

Figure 17. $8bn sales potential in the metastatic setting in the initial set of indications



Source: Citi Research

Figure 18. Herceptin revenues increased by 30% due to usage in multiple lines of therapy. We expect similar for checkpoint agents

	Adjuvant	Metastatic	Total
Cost per month ($)	4,166	4,166	4,166
Drug actual selling cost	100%	100%	100%
Suggested treatment time (months)	12	8	10.4
compliance	80%	80%	80%
Total Cost per patient ($)	**39,994**	**26,662**	**34,661**
% of Total Patients	60%	40%	100%
Number of patients	**27,881**	**18,587**	**46,468**
Patients who have insurance	85%	90%	87%
Patients who are eligible	90%	90%	90%
Implied users of Herceptin	**21,329**	**15,056**	**36,384**
Implied Herceptin Revenue	**853**	**401**	**1,261**
Roche income from herceptin in US in breast cancer	989	659	1,648
Revenue multiplier from multiple lines of metastatic therapy			**131%**

Source: Citi Research, Company Data

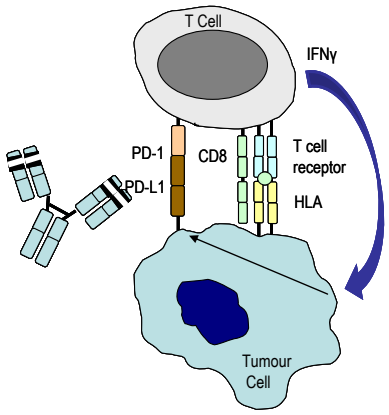
Figure 19. $8bn sales potential in the metastatic setting in the initial set of indications

Metastatic Setting	US	EU-5
no of drug-treated pts in metastatic setting (1st line)		
NSCLC	72,000	93,000
RCC	15,100	13,000
Melanoma	8,900	9,200
	96,000	**115,200**
%PD-L1 expression		
NSCLC	50%	
RCC	20%	
melanoma	40%	
No of metastatic pts with PD-L1 expressions		
NSCLC	36,000	46,500
RCC	3,020	2,600
Melanoma	3,560	3,680
Total no of PD-1 expression in metastatic setting	**42,580**	**52,780**
Cost of treatment (per annum)	**$110,000**	**$80,000**
Penetration	**70%**	**50%**
Duration of treatment (years)	**1.5**	**1.5**
Sales potential ($m)	**4,918**	**3,167**
NSCLC	*4,158*	*2,790*
RCC	*349*	*156*
melanoma	*411*	*221*

Source: Citi Research, Company Data

Combination therapy broadens the percentage of addressable cancer indications driven by epitope spreading and induced expression of immune related antigens

Figure 20. PD-L1/ PD1 binding induces immune tolerance of the T cell. IFN gamma induces PD-L1 expression

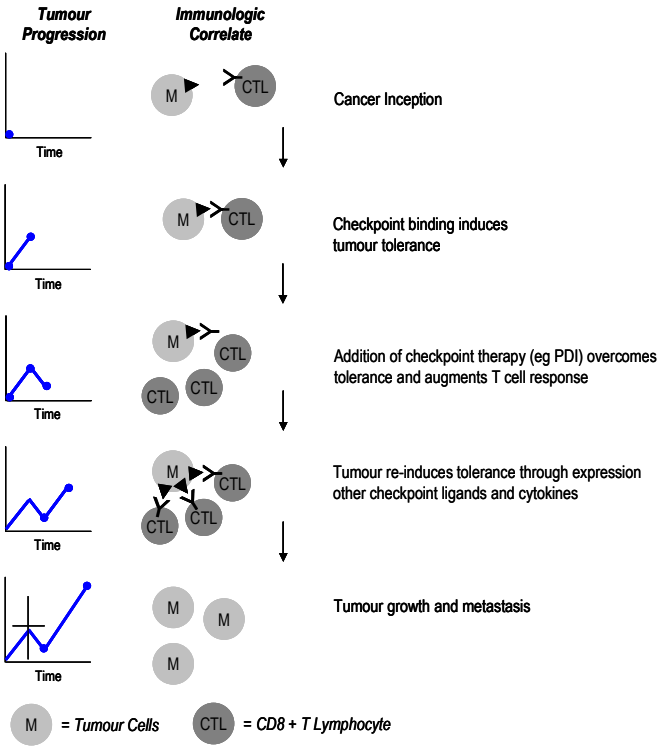


Source: Citi Research

The likely key driver for the expansion of indications for immune checkpoint agents is the use of these agents in combination therapies. These include combinations with existing cancer therapeutics (chemotherapy, TKIs, radiotherapy, cryotherapy, monoclonal antibodies), but also combinations of checkpoint inhibitors with other active immunotherapies (double checkpoint therapy, checkpoint with cancer vaccines, checkpoint with adoptive T cell therapy etc). Potential combinations are shown schematically below.

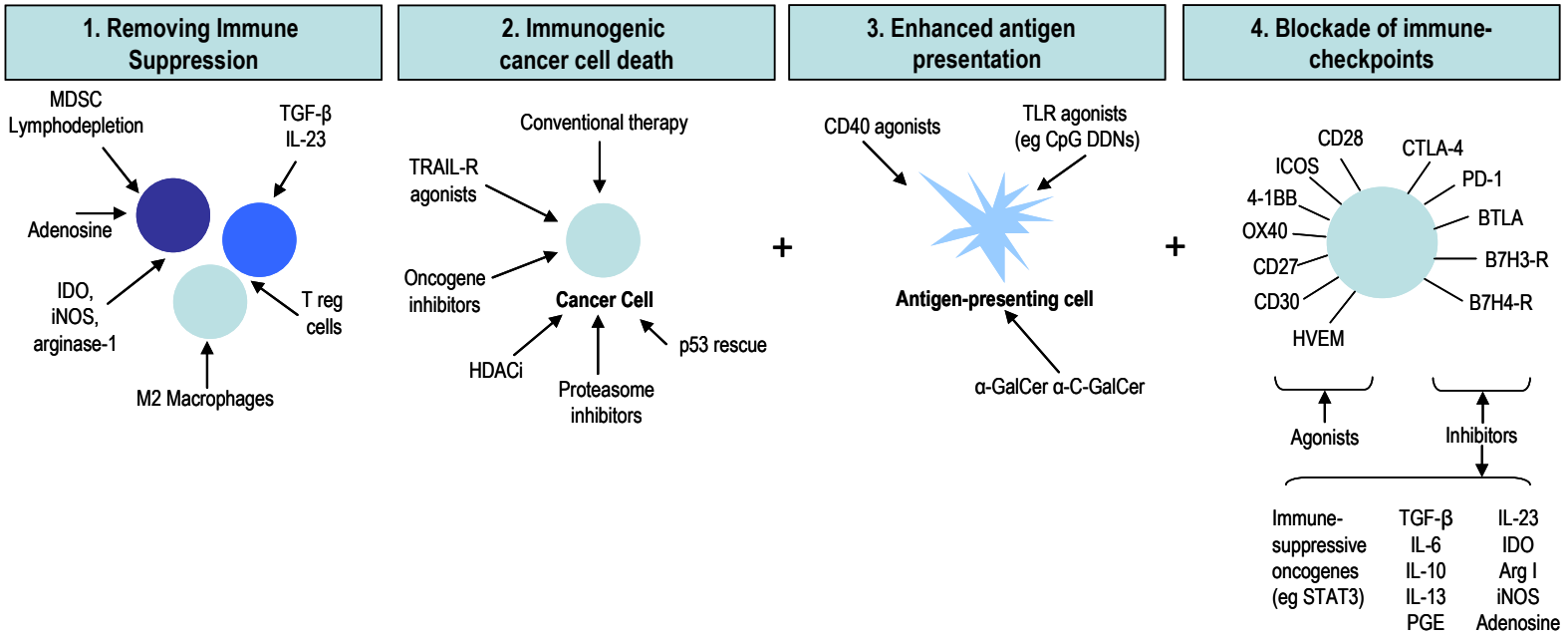
Combination immunotherapeutic based approaches should increase response rates and survival through epitope spreading. Epitopes are localised regions on the surface of antigen that can elicit an immune response**.** Epitope spreading is a process whereby epitopes distinct from, and non-cross-reactive with, an inducing epitope become major targets of an ongoing immune response. While this phenomena is thought to be causal in autoimmune diseases, in the field of immunotherapy it is highly desirable as it broadens the immune response against the tumour and limits the tumour's ability to evade the immune system. Co-administration of agents such as chemotherapy, radiotherapy or TKI can precipitate increased antigen expression on cancer cells and/or apoptosis (cell death) of the cancer cell. Both generate an expansion of liberating neo-antigens. The combination of an increase in neo-antigen expression therefore augments immunotherapy mediated activity by reducing the ability of the cancer cell to evade the immune system. Maximally effective combination strategies will likely require activity across four distinct nodes shown in Figure 22. We estimate that the adoption of combination modalities will increase the percentage of immunotherapy addressable cancer to at least 60% over the next 10 years.

Figure 21. How checkpoint agents cause tumour regression and how the immune system overcomes them. Most tumours require immunotherapy as part of a combination to address tumour escape mechanisms.



Source: Citi Research

Figure 22. Immunotherapy combinations can be assembled from four buckets



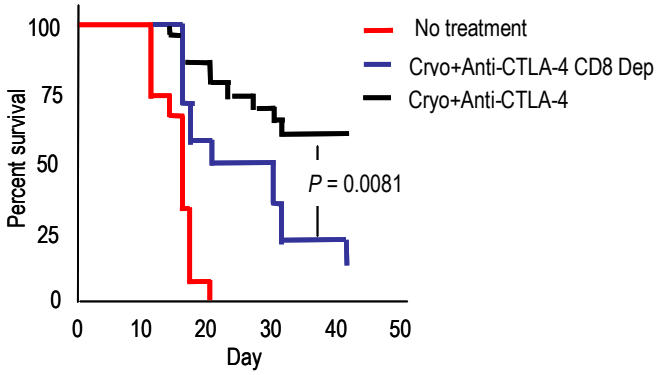
Source: Citi Research

Small, but growing, evidence that combining a checkpoint agent with other forms of chemotherapy materially improves response rates and survival

While there is significant pre-clinical data supporting combination immunotherapy, there is relatively little published data to date in the clinical setting. An interim analysis of a phase I trial to be presented at ASCO with nivolumab showed a response rate of 33% with nivolumab in combination with doublet first line chemotherapy in patients with 1st line NSCLC. This compares favourably with chemo doublet therapy alone (c.25-27% response rate). Importantly, we suspect that the updated response rates to be presented at ASCO will likely be higher than the 33% reported in the ASCO abstracts given the latency of PD1 activity.

Separately, data to be presented at ASCO showed that adding Yervoy to brain surgery for melanoma brain metastasis was associated with an increase in median survival from 6.8 months to 28.3 months in the Yervoy-treated group. We assume that the radiotherapy increases epitope spreading through direct apoptosis of malignant cells, broadening and deepening the immune response elicited by Yervoy

Figure 23. Yervoy significantly increased overall survival in xenograft models of breast cancer when combined with cryotherapy to induce epitope spreading.



Source: Cancer Res; 72(2) January 15, 2012, Citi Research

Subgroup analysis of START data with Merck Serono's Stimuvax provides indirect support for the potential importance of epitope spreading and immunotherapy.

We have previously cited the recent positive subgroup analysis from the recently announced failed phase III start trial with Stimuvax in NSCLC. There was a statistically significant (p=0.016) 22% reduction in the *post hoc* subgroup analysis of NSCLC patients treated with Stimuvax who had received initial concurrent chemoradiotherapy compared to patients in the control arm. Although Merck will likely not be able to secure approval solely on this data, the positive signal demonstrates the potential important of concurrent immuno/traditional therapies in increasing immunogenicity, likely through a broader activation of the immune system (presumably through epitope spreading, see page 19).

Anti-PD1 vs. Anti-PDL1? It's not what you have, it's the way you use it….

Despite BMY's 2-year lead time on Roche and Merck, and BMY's broad portfolio of immunotherapy-related assets, we see Roche as highly competitive given its significant experience in oncology, its antibody engineering expertise and its greater financial ability to conduct parallel clinical development programs given its $8bn per annum annual R&D expense compared with BMY's c.$4bn. We are more cautious on the outlook for MRK's anti-PD1 given its lack of oncology legacy and anecdotal reports of drug-related wasting potentially associated with the agent. AZN remains a potential long-term competitor given its rapidly accumulating portfolio of immunotherapy assets. We believe that the difference in development programs and combination strategies are much more significant than likely differences in PD1/PD-L1 backbone.

The PD-1 vs. PD-L1 debate is likely a red herring. In our view, the key issue is the vastly underappreciated market potential for the class, regardless of agent.

The PD-1 vs. PD-L1 debate is likely a red herring, we believe. Roche and AZN are developing antibodies to the PD-L1 ligand expressed on the surface of many tumour cells. BMY and Merck are developing anti-PD1 antibodies targeting receptors located on the T cell. In our view, the key issue is the vastly underappreciated market potential for the class, regardless of agent. In terms of differentiation of agents within the PD1/PDL1 axis, we believe that the competitive positioning is less dependent on molecular differences in profile but instead will be determined by non drug-specific issues such as (i) trial design; (ii) ability to development combination based approaches; (iii) application of diagnostic biomarkers to enrich clinical trials; and (iii) financial resources to run parallel trials.

Roche's anti-PDL1 seems to have broader efficacy, and better adverse event profile than BMY's PD1

Roche's PD-L1 likely better tolerated but comparative efficacy unclear. In contrast to Merck and BMY, Roche is developing an anti-PD-L1 (MPDL3280A) which targets the PD-L1 receptor. We anticipate that Roche's PD-L1 will have a lower level of drug-related pneumonitis than seen with nivolumab. Pneumonitis was seen in 1% of patients with nivolumab and resulted in 3 deaths in the phase II data. In contrast to nivolumab, selective PD-L1 blockade has no effect on PDL2 signaling in the lungs, maintaining local tolerance and protection of pulmonary tissues, and has not been associated with any grade 3/4 drug-related cases of pneumonitis. BMY's nivolumab blocks PDL2 on the lung tissue from binding to the PD1 receptor on the T cells resulting in impaired self tolerance and increased probability of drug-related pneumonitis

Disadvantages include possibly lower numerical response rates seen in data to date and its IgG1 isotype which is more prone to cytotoxicity (ADCC)

Potential disadvantages of Roche's MPDL3280A. There are two key points of debate in relation to Roche's anti-PDL1: i) potential disadvantages of PDL1 blockade and ii) potential disadvantages in relation to Roche's IgG1 isotype. The cross-trial comparison for numerical response rates for both Roche and BMY anti-PDL1 (on hold) targeted antibody look inferior to those demonstrated by anti-PD1 agents. Anti-PDL1 antibodies fail to block PDL2 binding, which has been implicated in the pathogenic process in mice (although its role in humans is unclear). We caveat the dangers of cross-trial comparisons, especially for small phase I/II data.

Separately, the levels of ATA (anti-therapeutic antibodies) are much higher with Roche's PDL1 compared with BMY PD1 necessitating dosages at or higher than 10mg/kg compared with responses with BMY nivolumab seen at 3 mg/kg. The likely higher dosing for Roche's PDL1 compared with nivolumab has potential cost and safety disadvantages — however its clinical significance appears minor given evidence to date. Separately, the IgG1 isotype used for Roche's MPDL3280A is more likely to elicit an unhelpful ADCC (antibody-dependent cell mediated cytotoxicity) potentially negatively impacting its therapeutic effect by inducing cell death of cytotoxic T cells. Both Merck and BMY's anti-PD1 are the IgG4 isotype associated with lesser levels of activation of ADCC.

..but Roche's anti-PDL1 could have a broader spectrum of activity in monotherapy. Despite the scientific hypothesis arguing for a lower efficacy for Roche's PD-L1, Roche's phase I data in NSCLC, melanoma and renal cancer looks broadly comparable to that presented by Merck and BMY given the relatively small patient numbers and dose-ranging nature of the trial. In addition, we note that, Roche's PD-L1 has also demonstrated responses in gastrointestinal, pancreas and urological tumours, which have not been demonstrated with the anti-PD1 agents to date.

Reports of anorexia and wasting related to MRK's lambrolizumab – unclear whether related to the drug's mechanism of action

Potential Differences between anti-PD1. Even within the PD1 antagonists, we anticipate the agents to have different safety and efficacy profiles dependent on both the nature of epitopes and the ability to activate the innate immune system through ADCC. We note that Merck's lambrolizumab reported a much lower adverse event rate in its early data compared with BMY's nivolumab, potentially related to re-engineering the Fc end of the molecule. Separately, we have previously highlighted 3 case reports on potential drug related anorexia association with MRK's lambrolizumab. However, it is unclear if this is related to the mechanism of action of the drug.

Roche's development plan is more aggressive than BMY. Roche has fewer financial constraints to fund parallel development

Unsurprisingly, given its annual R&D expense and oncology expertise, we understand that Roche is taking the most aggressive and fastest approach to commercialise its anti-PDL1 asset. Following presentation of the 300 patient phase I data at ASCO in multiple tumour types, we anticipate Roche to initiate multiple phase III programs in renal, melanoma, and NSCLC indications, as well as exploratory phase I/II combination trials with TKI/ chemotherapy and radiotherapy. Unlike BMY, Roche has indicated its intent to recruit only patients whose tumours express a certain threshold levels of PD-L1 at initiation of therapy. While Roche may be reducing its potential market, this enrichment strategy is likely to result in abbreviated clinical development versus current standard of care, allowing Roche to close the gap with nivolumab to as little as perhaps 15 months. We anticipate that BMY and Roche will attempt to file prior to the completion of the phase III programs, using both response rates and interim survival analysis. Overall response rates and overall survival are co-primary endpoints within the ongoing phase III programs.

Biomarkers under development. Data presented at ASCO 2012 suggested that PD1 expression is a minimal determinant for response to a PD1/ PD-L1 molecule with 0 objective responses in tumours lacking material PD-L1 expression and 9 (36%, p=0.006) responses in tumours with higher expression patterns[1]. The dynamic nature of PD1 expression in relation to the immunogenic progress makes PD1 expression a relatively unsatisfactory biomarker. Importantly, PDL1 expressions vary greatly within both the primary and metastatic site. In addition, levels of PDL1 expression fluctuate in response to treatment and disease progression.

[1] Topalian et al. N Engl J Med 2012;366:2443-54.

Building the anti-PD1/ PDL1 market model

Advanced lung, melanoma and renal cancer will drive at least $8bn sales as monotherapy in first indications

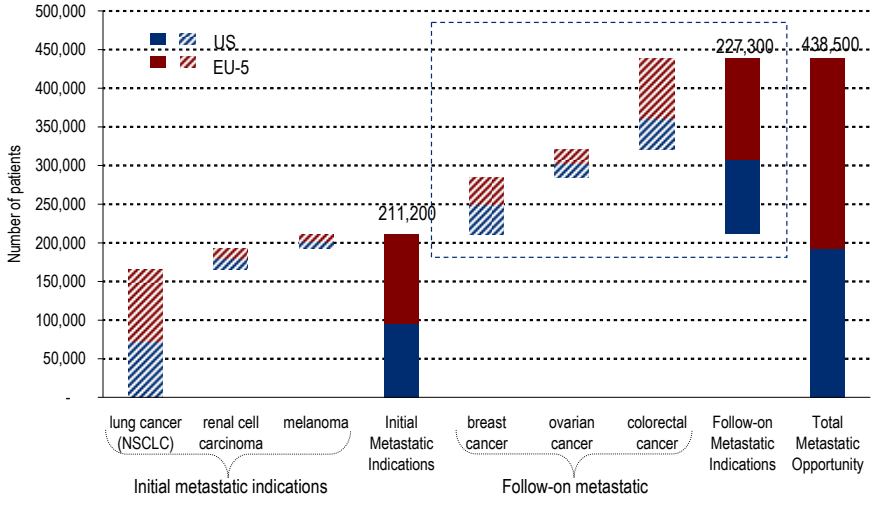
Advanced lung, melanoma and renal cancer should drive $8bn sales as monotherapy in first indications. We anticipate that PD1/ PD-L1 agents will form the standard of care for at least 50% of patients with these cancers who also express PD-L1. We calculate market potential of c.$8bn. Our forecasts assume a price per patient of $110,000 per year and an average of 18 months therapy per patient in the US. Ex-US, we assume a reimbursement price of $80,000 per patient. These prices are in line with the reimbursed price of Yervoy currently. Our forecasts are shown in Figure 17. While typically we are pessimistic over the EU's ability to reimburse premium priced oncology assets, we believe Yervoy-like efficacy in >35% of treated patients is likely to secure high levels of reimbursement (albeit a lower price) given the anticipate impact on survival [2].

Adjuvant and repeated cycles in metastatic setting provide call option

Adjuvant and repeated cycles in metastatic setting provide call option. Our forecasts include no contribution for the use of PD1 in either adjuvant (curative setting) or multiple lines of use in the metastatic setting. Roche has disclosed that partial responses attained with anti-PD1 can prove durable through a second cycle of treatment. We note that PD-L1 levels on cancer stem cells have been reported at low levels, likely reducing the probability that PD1 and PD-L1 mediated agents will have a material impact in reducing disease recurrence in the adjuvant setting.

Combination therapies will drive indication expansion, price inflation and increased duration/cost of treatment. As we have previously described, pre-clinical data indicated that the many cancers can be converted to responsive to immunotherapy through the use of multi-modality combination therapy. We anticipate these strategies will expand the use of immunotherapies, especially checkpoint inhibitors to large high population cancers such as breast and GI, which have shown limited responsiveness to checkpoint agent monotherapy to date.

Figure 24. Additional indications could provide an opportunity equally large as the initial ones



Source: Citi Research

[2] Although we have PD-L1 expression as the basis for our market size calculations, we suspect that PD-L1 baseline expression (as a predictive marker for anti-PD1/PDL1 efficacy) will become increasingly irrelevant as the use of checkpoint agents migrates from mono to combination therapy.

The real driver for market creation for anti-PD1/L1 class is combination therapy

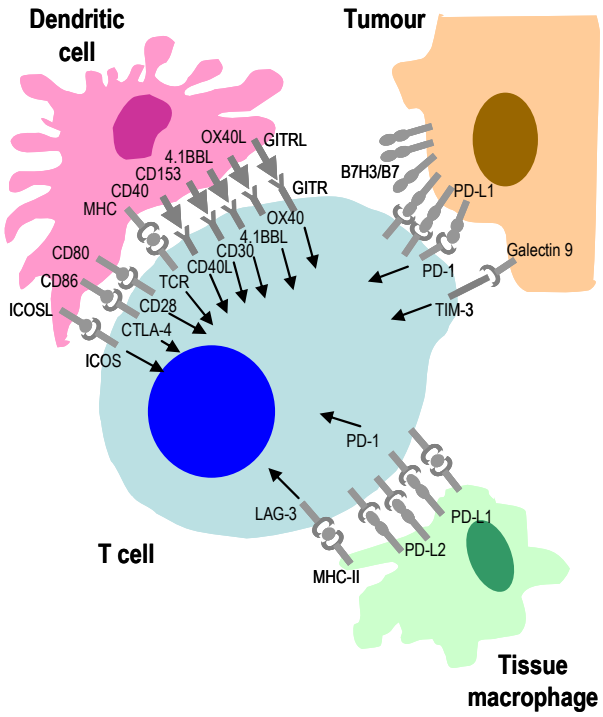
Yervoy — PD1/PD-L1 combinations manageable but superior toxicity profile likely favours 2nd generation checkpoint agents. While initial attempts to administer Yervoy and nivolumab systemically in combination led to significant immune-related adverse events (we expect pilot phase II data to be presented at ASCO 2013), we understand that sequencing, dose adjustment and intra-tumoural Yervoy administration can materially lower the incidence of immune related adverse events. Pre-clinical and clinical data supports the notion that prior Yervoy administration can prime the immune response to a PD1/ PD-L1 based stimulus, increasing the percentage of patients experience a meaningful clinical benefit. BMY has already indicated that it intends to open a phase III combination trial. As we discuss in detail in the following section, we believe that Yervoy will likely be superseded by other immuno-modulators with less problematic immune-related adverse event profiles when used in combination with PD1/PDL1 treatment modalities.

Co-modulatory agents- potentiating anti-PD1 efficacy and increasing revenue/ patient

Novel/ novel immuno-modulator combination trials are already underway

Novel/novel immuno-modulator combination trials are already underway. The industry will quickly initiate pilot combination trials with novel/novel immuno-modulators as soon as PD1 dosing and safety in monotherapy is established in the concluding large phase I trials. We note that BMY already has a combination trial of its anti-KIR and nivolumab, anti-PD1 in three phase II program. We expect others to follow quickly. As Figure 25 demonstrates, there are multiple co-inhibitory and co-stimulatory molecules in development designed to overcome PD1/PDL1 resistance. These include "brake" mediated anti-LAG3, anti-Tim3 and "accelerator" mediated anti-CD137, anti-OX40. We anticipate the industry to use multiple factorial trials in multiple indications to indentify optimal combinations for given indications.

Figure 25. Costimulatory and coinhibitory ligand receptor pairs that are amenable to manipulation with immunostimulatory mAbs.



Source: Immunostimulatory Antibodies and Their Combination, Clin Cancer Res; 19(5) March 1, 2013, Citi Research

The main challenge to novel/ novel immuno-modulator therapy is minimising adverse events

The key barrier to successful development of combination is the increased risk of serious immune-related adverse events. Yervoy and nivolumab phase II combination data will be presented at ASCO showing synergistic response rates, but with significant immune-related toxicities, especially enterocolitis. Immune-related adverse events can be minimised or better managed through a combination of strategies including:

1. dose scheduling — sequential vs. combination use;
2. local intra-tumoural administration to minimize dosing;
3. superior targeting through concomitant MAb administration;

4. patient stratification;
5. optimised combinations;
6. earlier detection of immune related adverse events and/or superior management.

Pre-clinical/ early clinical data for novel combinations is very encouraging. We focus on three in this report anti-LAG3 and anti- KIR (both immuno-inhibitory) and anti-CD137 (anti-1-4BB) and anti-OX40 (immuno-stimulatory)

While there is scarce clinical data for any immuno-modulator combination to date, the preclinical data is very promising. While Yervoy and PD1 combination receives the bulk of investor attention, we believe that the second generation MAbs will likely become the dominant preferred combination with PD1/ PD-L1 backbones. Exhibit 25 outlines novel classes of immuno-inhibitory and immuno-stimulatory molecules in development for blood and solid tumours. We focus on four in this report: anti-LAG3 and anti- KIR (both immuno-inhibitory); anti-CD137 (anti-1-4BB) and anti-OX40 (immuno-stimulatory)

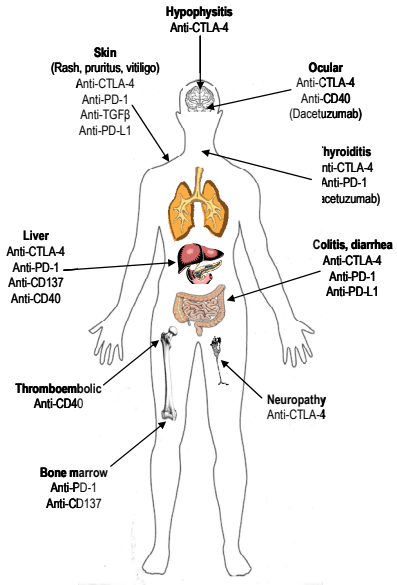
Novel Co-immune-inhibitory agents

Anti-LAG-3 is about to enter combination trials with BMY's nivolumab

Anti-LAG-3 is about to enter combination trials with BMY's nivolumab. LAG-3 has been suggested to directly modulate the activity of PD-1+ cells. Co-expression of LAG-3 and PD-1 has been demonstrated in malignant mouse and human tissue. A significant percentage of CD4+ and CD8+ TILs from transplanted B16 melanoma, MC38 colorectal adenocarcinoma, and Sa1N fibrosarcoma expressed high levels of LAG-3 and PD-1, whereas similar up-regulation was not observed on peripheral T cell populations.

Combination treatment of Sa1N fibrosarcoma and MC38 colorectal adenocarcinoma with anti-LAG3 and anti-PD1 in xenograft mice models was associated with complete responses in 70-80% of mice after 50 days with minimal evident toxicity (see Figure 28). Monotherapy with either anti-PD1 or anti-LAG3 had only modest effects. We anticipate that BMY will shortly initiate a clinical trial program with anti-LAG3 in combination with its anti-PD1, nivolumab.

Figure 26. Immuno-related adverse events is the major hurdle for combination immuno therapy



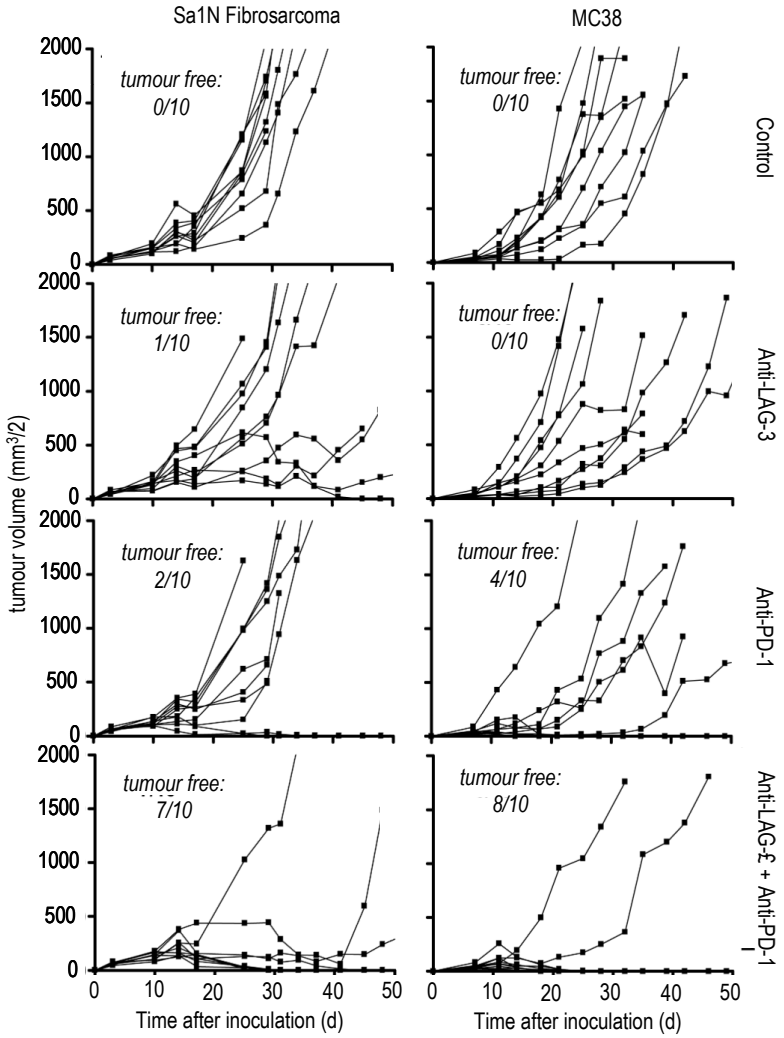
Source: Citi Research, Company data, Clinicaltrials.gov

Figure 27. TNF family members targeted for cancer immunotherapy, their expression patterns, and therapeutic targeting molecules

Molecule	Expressed by	Expression level	Therapeutic targeting molecule	Molecule	Expressed by	Expression level	Therapeutic targeting molecule
OX40 (CD134)	CD4+, CD8+ T cells, NK cells, NKT cells, Foxp3+ Treg cells	Inducible on most cells, constitutively expressed on Treg cells	MEDI6469 (mouse-anti human OX40 agonist mAb)	OX40L (CD252)	APCs, endothelial cells, smooth muscle, mast cells	Inducible on all cells described	N/A
GITR (CD357)	CD4+, CD8+ T cells, NK cells, NKT cells, B cells, Foxp3+ Treg cells, Macrophages, DCs	Inducible on most cells described, constitutively expressed on Treg cells	TRX518 (anti-human GITR mAb)	GITRL	APCs, endothelial cells	Constitutively expressed	N/A
4-1BB (CD137)	CD4+, CD8+ T cells, NK, NKT, mast cells, neurophils, Foxp3+ Tregs, DCs, enothelial cells, eosinophils,	Inducible on most cells, constitutively expressed on Treg cells	BMS-666513 (humanized anti-human 4-1BB mAb)/ PF-05082566 (humanized anti-4-1BB mAb)	4-1BBL	APCs, mast cells, NK cells, smooth muscle, hematopoietic progenitors	Primarily inducible, constitutively expressed by hematopoietic progenitors.	N/A
CD40	APCs, epithelial, endothelial, and smooth muscle cells, fibroblasts, basophils	Both constitutive and inducible expression	4D11 (anti-human CD40 mAb)	CD40L (CD154)	T cells, B cells, Eosinophils, monocytes, macrophages, endothelial, epithelial, and muscle cells	Inducible on all cells described	Recombinant CD40L
CD27	CD4+, CD8+ T cells, some B cells, Foxp3+ Treg cells, NKT cells, hematopoietic	Usually constitutively expressed on T cells, inducible on B cells	CDX1127 (agonist anti-CD27 mAb)	CD70	T cells, B cells, DCs, APCs	Induced on lymphocytes and constitutively expressed by APCs	SGN-75 (antibodydrug conjugate targeting CD70+ tumour cells)

Source: Current Opinion in Immunology 2013, 25:230–237, Citi Research

Figure 28. Anti-LAG3 antibodies showed significant activity in colorectal and fibrosarcoma mouse models when combined with an anti-PD1 backbone



Source: Citi Research , Woo et al. Cancer Res 2012 Feb 15

BMY's anti-KIR is already being evaluated in 420 patients in combination with nivolumab

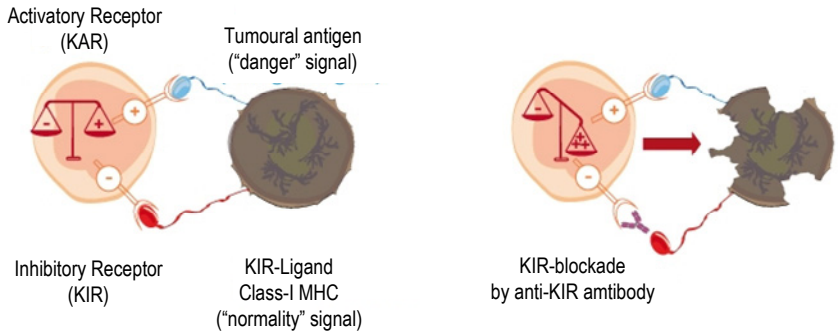
Anti-KIR. BMY's/ Innate Pharma's lirilumab (IPH2102/BMS-986015) is currently being tested in over 420 patients for both blood and solid tusmours. Lirilumab is a fully human monoclonal antibody blocking interaction between Killer-cell immunoglobulin-like receptors (KIR) on NK cells with their ligands. Lirilumab aims at "unblinding" NK cells and facilitating their activation by blocking their inhibitory receptors. BMY is testing their anti-KIR in combination with nivolumab and Yervoy in solid tumours and testing it as monotherapy in AML. Pre clinical data suggests low levels of cytokines release potentially allowing it to be safely combined with both Yervoy and nivolumab. We anticipate first data in 2014 about the magnitude and durability of responses for the nivolumab combination trial. Separately, we understand that Genentech has an anti-KIR in late pre-clinical development and is seeking to develop combinations with Herceptin and Rituxan. Anti-Kir mediated activated NK cells are thought to bind the Fc end of bound Herceptin and Rituxan (ADCC).

Figure 29. Combination trials of anti-KIR antibody

Phase	Patient No.	Primary Comp.	Indi-cation	Comb-ination
I	150	Aug-15	Solid	+nivolumab
I	125	Jul-13	Solid	+Yervoy
II	150	Jun-16	Solid	-

Source: Citi Research, clinicaltrials.gov

Figure 30. Schematic showing KIR blockade by anti-KIR antibody



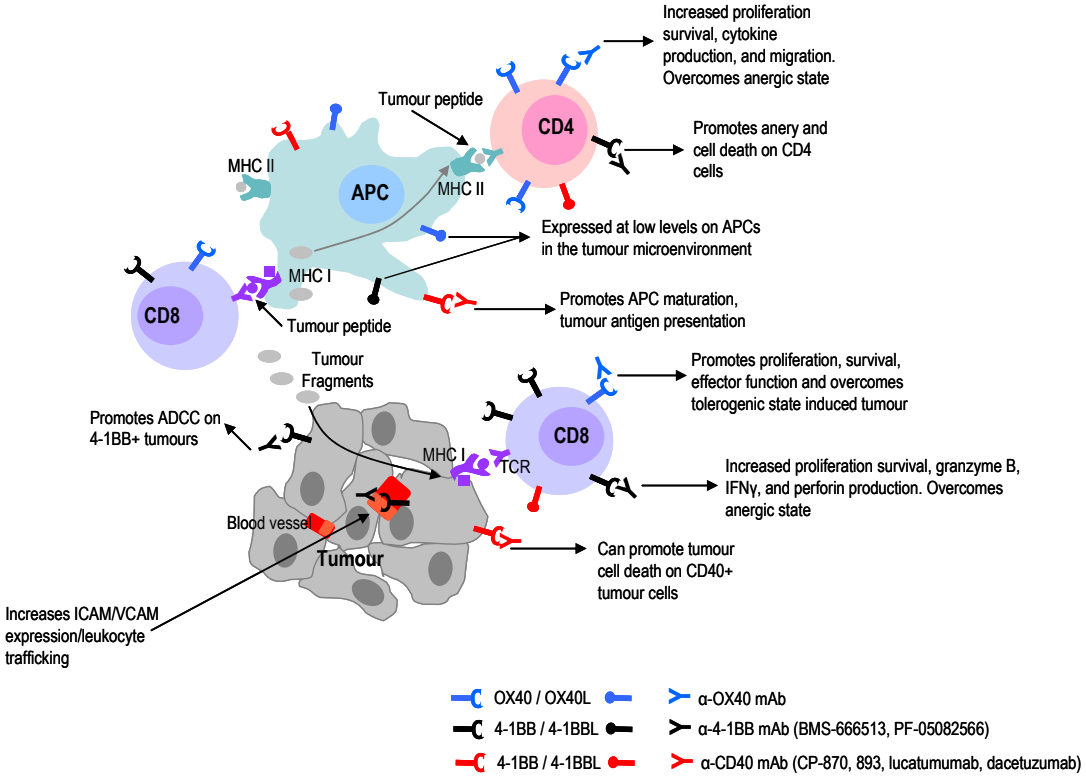
Source: Citi Research, BMS Data

Co-immuno-stimulatory agents

Both PFE and BMY have anti-CD137 in phase I trials as mono and combination therapy.

Both BMY and PFE have anti-CD137 monoclonal antibodies to CD137/ 4-1BB in development as mono and combination therapies .Urelumab is a fully human anti-4-1-BB antibody targeting the CD137 receptor. CD137 is up-regulated on activated lymphocytes, NK cells and dendritic cells and plays an important role in the potentiation of antigen-specific immune responses as well as in antibody-dependent cell-mediated cytotoxicity (ADCC). Binding of the agonist antibody to CD137 receptor can reverse tolerance of CD8+ T cells and promote regression of established tumours primarily via CD8-CTL activity and NK cell function.

Figure 31. The TNFRs OX40, 4-1BB, and CD40 as targets for cancer immunotherapy



Source: Moran, Kovacsovics-Bankowski and Weinberg, Current Opinion in Immunology 2013, 25:230–237, Citi Research

Anti-CD137 may induce T cell memory, initiate cytotoxic effects on cancer cells as well as enhancing tumour accessibility.

The antitumour immune effects of agonist 4-1BB antibody therapies are CD8 dependent and promote long-term antitumour memory T cell survival. Thus, targeting 4-1BB may be a viable approach to promoting tumour antigen-specific T cell responses. There is some debate over the mechanism of 4-1BB mediated monotherapy as it seems to have multiple mechanisms of action:

- the activation of 4-1BB enhances immune cell activation
- 4-1BB activation seems to enhance the accessibility of the tumour by lymphocytes through an ICAM-1 and VCAM-1 mediated pathway. Treatment of tumour-bearing mice with a 4-1BB agonist mAb increased infiltration of activated T cells
- The potential expression of CD137 on the tumour surface may allow for direct tumour cell death via antibody dependent cell mediated cytotoxicity (ADCC) and tumour cell phagocytosis

Urelumab (BMS-663513), a fully humanised IgG4 anti-CD137 mAb, was tested in a phase I dose-escalation study in patients with advanced cancer. The study, presented at the 2008 ASCO meeting, showed three partial responses and stable disease in four patients with melanoma. Preliminary biomarker analysis revealed an increased percentage of activated CD8+ T cells in the peripheral blood.

Lower dose of BMY's anti-CD137 urelumab necessitated given hepatoxicity seen in early phase I trials

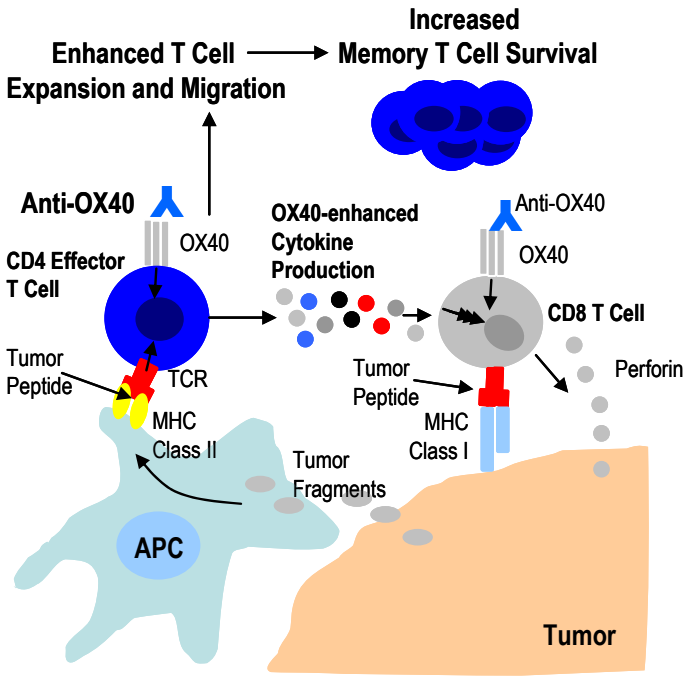
A second-line phase II monotherapy trial of urelumab in subjects with previously treated unresectable stage III or IV melanoma was terminated due to a high incidence of grade 4 hepatitis. BMY has since re-entered clinical trials with urelumab with lower dosing combined with co-administration of Rituxan in order to localize NK activation to CD19 expressing cells. PFE is running a 78 patient phase I/II trial with PD566 in patients with CD20 NHL. We anticipate data in late 2014, early 2015 respectively. Both BMY and PFE are exploring whether the co-administration of Rituxan can materially reduce hepatotoxicity and simultaneously bolster efficacy. Administration of anti-CD20 (Rituxan) and/or anti-Her2 (Herceptin) leads to selective up regulation of CD137 ligands on T and NK cells in the vicinity of the tumour body, leading to localized CD137 induced immune activation, allowing lower dosing and potentially eliminating the hepatotoxicity seen at higher dosing.

Assuming the co-administration of the Rituxan obviates hepatotoxicity, anti-CD137 could become an adjunct to antibody directed therapy for both blood and solid tumours. B cell malignancies such as NHL, CLL are obvious targets but potential future directions include malignancies where there is tumour-specific antigen expression such as Her2 in breast and gastric cancer, mesothelin expression in hepatocellular, pancreatic and ovarian cancer.

Anti-OX40 monoclonal and fusion proteins are under development from AZN/ Medimmune (licensed from Agonox)

Anti-OX40 monoclonal and fusion proteins are under development from AZN/ Medimmune (licensed from Agonox) with others in late pre-clinical development. Binding of the TNF receptor family co-stimulatory molecule OX40 (CD134) with an agonist anti-OX40 mAb enhances anti-tumour immunity by augmenting CD4 and CD8 T cell clonal expansion, and effector differentiation, as well as turning off the suppressive activity of FoxP3+CD4+ regulatory T cells (Treg). OX40 is of particular interest as a therapeutic target as it is not expressed on naïve T cells but rather, is transiently up-regulated following TCR stimulation.

Figure 32. Modified schematic showing anti-OX40 mechanism of action



Source: Citi Research, Company data

Anti-OX40 seems to require combination therapy to demonstrate strong efficacy signals. Monotherapy with anti-OX40 has shown limited efficacy, particularly against poorly immunogenic tumours in animal models. The balance of activity seems to be determined by the ratio of IL2 to TGFbeta (high is better for anti-OX40 activity). A less favourable tumour context can be overcome by co-administration with IL2 which allows the expansion of CD4 effector cells but does not increase the activity of number of immunosuppressive Treg cells. Combined anti-OX40/anti-CTLA-4 therapy significantly enhanced tumour regression and survival of TRAMP-C1 prostate or MCA-205 sarcoma tumour-bearing hosts.

We note that AZN/Medimmune recently suspended their ongoing phase 1 trial program with their anti-OX40. Medimmune has developed a high affinity fusion protein to eliminate neutralizing antibodies that occurred with the initial anti-OX40 antibody. In addition, we understand that Medimmune is also humanising the original antibody to eliminate the neutralising antibodies while preserving a longer half life. We suspect that one or perhaps both antibodies are likely to be taken into development both as single agents, and more likely as combinations with AZN's anti-CTLA4 agent, tremelimumab, their anti-PDL1 antibody MEDI-4736 and possibly also in combination with the cytokine IL2.

Figure 33. Toxicity, positive comments, and caveats pertaining to immunomodulating mAbs

Agent	Toxicity	Positive comments	Caveats
Ipilimumab (anti–CTLA-4; refs. 12, 13)	sh, colitis, diarrhea, hepatotoxicity, endocrinopathies, neuropathies	Two randomized phase III trials showed improvement in OS in patients with melanoma as first- and second-line therapy. First therapy ever to show a survival improvement in metastatic melanoma.	More efficacious schedule and dosage to be defined. Increase in tumour lesion size due to lymphocyte infiltrates might be confused with disease progression and makes decision making difficult. Lack of predictive biomarkers.
Tremelimumab (anti–CTLA-4; ref. 18)	Colitis, diarrhea, rash, pruritus, endocrinopathies	Treatment schedule with administrations every 90 days (too long interval) with the same safety profile as ipilimumab. Confirmed clinical activity in some patients.	Negative results in the melanoma phase III study, compared with standard chemotherapy.
Nivolumab (anti–PD-1; refs. 42–44)	Relevant toxicity is uncommon. Some patients develop fatigue, rash, diarrhea, pruritus, pneumonitis; rare decreases in appetite and hemoglobin, pyrexia.	Dramatic and sustained clinical responses in 20%–30% of patients with melanoma, renal cell cancer, and non–small cell lung cancer. Effective at low doses (1 mg/kg). Better safety profile as compared with ipilimumab and tremelimumab.	Not yet studied in phase III trials. Lack of confirmed biomarkers (PD-L1 expression under study, pending confirmation).
MK-3475 (anti–PD-1; ref. 46)	Fatigue, pruritus, dyspnea, nausea, anorexia	Promising efficacy and safety profile (no grade 3–4 adverse events in the phase I trial)	Early phase of development.
BMS936559 (anti–PD-L1; ref. 108)	Fatigue, infusion-related reaction, diarrhea, arthralgia, rash, nausea, pruritus	Theoretically a better inhibition PD-1/PD-L1 because directly inside the malignant tissue (where there is the higher PD-L1 expression from the tumour and PD-1 expression on TILs). Good safety profile.	Early phase of development.
Anti-CD40 (58) Dacetuzumab (67)	Cytokine release syndrome, thromboembolic syndromes, transient cytopenias, depletion of T cells in multidose trial	CP-870,893 has shown clinical efficacy in a number of settings for patients with advanced cancer. Dacetuzumab has shown single-agent activity in DLBCL. No tumour regression was observed in multiple myeloma Possible combination with a checkpoint blockade MAbs (i.e., anti–CTLA-4, anti–PD-1), as well as rituximab, and chemotherapuetic agents.	It is necessary to improve our understanding of the mechanism of action of different CD40 mAb and understand which of the many mechanisms is the most appropriate for the clinical use.
Urelumab (anti-CD137; ref. 31)	Fatigue, rash, fever, rare cytopenias, and hepatotoxicity.	Possible combination with anti-immune checkpoint blockade MAbs (ipilimumab, nivolumab).	Severe hepatic toxicity (seems dose related, not observed at lower doses). Early phase of development.
Anti-OX40	Fatigue, transient lymphopenia	Excellent for combination with other molecules.	Early phase of development.
Anti-TGF-b (GC1008) Fresolimumab (109)	Rash, gingival bleeding, SCC, keratoacanthomas	Promising result in phase I trial.	Early phase of development.

Source: Clin Cancer Res; 19(5) March 1, 2013, Citi Research

Figure 34. Companies mentioned in this report

Company	Current price	Rating	Target price	% ETR
Allergan, Inc.	98.6	Buy	124.0	*26%*
Amgen Inc	103.8	Buy	133.0	*30%*
ARIAD Pharmaceuticals Inc	17.0	Buy	28.0	*65%*
AstraZeneca PLC	33.9	Neutral	30.0	*-6%*
Bayer AG	84.7	Buy	90.0	*9%*
Bristol Myers Squibb	44.1	Buy	55.0	*28%*
Celgene Corp	124.2	Buy	140.0	*13%*
Forest Laboratories, Inc.	38.0	Buy	44.0	*16%*
Gilead Sciences Inc	56.4	Buy	75.0	*33%*
GlaxoSmithKline PLC	17.4	Buy	18.1	*8%*
Incyte Corporation	23.0	NR	NR	*NR*
Johnson & Johnson Inc	88.2	Buy	95.0	*10%*
Eli Lilly	55.2	Buy	60.0	*12%*
Merck KGaA	119.4	Neutral	120.0	*2%*
Merck & Co	45.4	Neutral	44.0	*1%*
Novartis AG	72.4	Buy	83.0	*18%*
Novo Nordisk A/S	989.5	Buy	1,150.0	*19%*
Pfizer	28.6	Buy	31.0	*12%*
Roche Holding AG	251.0	Buy	300.0	*23%*
Sanofi SA	85.1	Buy	101.0	*22%*
Shire Pharmaceuticals	21.4	Buy	22.0	*4%*
Vical Inc	3.6	Buy	6.0	*64%*

Source: Citi Research, datacentral. NR=Not Rated

Glossary of Terms

Figure 35. Glossary of terms

Adjuvant therapy	Any secondary treatment for cancer (such as chemotherapy) given after the primary treatment (such as surgery) in order to remove residual microscopic disease. Typically refers to early stage/ potentially curable disease
Apoptosis	A process of programmed cell death by which cells undergo an ordered sequence of events which lead to death of the cell, as occurs during growth and development of the organism, as a part of normal cell aging, or as a response to cellular injury
B cell	A lymphocyte, developed in the bone marrow, that produces antibodies and is responsible for the immune system
Biomarkers	A substance used as an indicator of a biological state, most commonly disease
Bispecific	Whose properties or activities vary according to the specific biological molecule that it interacts with
CART-19	Engineered receptors, which graft an arbitrary specificity onto an immune effector cell. Typically, these receptors are used to graft the specificity of a monoclonal antibody onto a T cell
Checkpoint agents	Activated in response to diverse DNA-damaging agents and radiation, thus representing a critical barrier limiting or enhancing therapeutic efficacy
CLL	Chronic Lympocytic Leukaemia
CD (cluster of designation)	A protocol used for the identification and investigation of cell surface molecules providing targets for immunophenotyping of cells
Concomitant chemotherapy	Medical treatments at the same time as other therapies
CTLA4	A protein receptor that downregulates the immune system. CTLA4 is found on the surface of T cells, which lead the cellular immune attack on antigens
Cryotherapy	The local or general use of low temperatures in medical therapy. Cryotherapy is used to treat a variety of benign and malignant lesions
Cytokine	Any of various small regulatory proteins that regulate the cells of the immune system
Cytokine storm	Potentially fatal immune reaction consisting of a positive feedback loop between cytokines and immune cells, with highly elevated levels of various cytokines
EMA	European Medicines agency
End Stage patients	Patients during the final stages of life
Endothelial cells	The thin layer of cells that lines the interior surface of blood vessels and lymphatic vessels forming an interface between circulating blood or lymph in the lumen and the rest of the vessel wall
FDA	Food and Drug Administartion, responsible for protecting and promoting public health through the regulation and supervision of prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices
Hematopoesis	The formation of blood cellular components. All cellular blood components are derived from haematopoietic stem cells
Hepatotoxicity	Chemical-driven liver damage
IL2	An interleukin, a type of cytokine signalling molecule in the immune system. It is a protein that regulates the activities of white blood cells
Interferon (IFN)	Proteins made and released by host cells in response to the presence of pathogens such as viruses, bacteria, parasites or tumour cells. They allow for communication between cells to trigger the protective defences of the immune system that eradicate pathogens or tumours
Immunocompetency	The body's capacity to develop an immune response following exposure to an antigen
Immunogenicity	The ability of a particular substance to provoke an immune response
Immunoinhibitors	The inhibition of an immune response
Immunomodulator	A drug used for its effect on the immune system
Immunostimulators	Any substance that stimulates an immune response
Killer-cell Immunoglobulin-like Receptors (KIR)	A family of cell surface proteins found on important cells of the immune system called natural killer (NK) cells. They regulate the killing function of these cells by interacting with MHC class I molecules, which are expressed on all cell types
Macrophage	A white blood cell that phagocytises necrotic cell debris and foreign material, including viruses, bacteria, and tattoo ink. It presents foreign antigenson MHC II to lymphocytes. Part of the innate immune system
Mast cells	A resident cell of connective tissue that contains many granules rich in histamine and heparin
Metastatic	Cancer that has spread from the place where it first started to another place in the body
Monoclonal Antibodies (MAb)	A protein genetically engineered from a single clone of a B cell, especially one produced by fusion with a tumour cell and intended for use as a drug
Monotherapy	The transference of a bodily function or disease to another part of the body, specifically the development of a secondary area of disease remote from the original site, as with some cancers
Neo-antigen	A new specific antigen that develops in a tumour cell
NHL	Non-Hodgkin's Lymphoma
NK cells	Natural killer cells are a type of cytotoxic lymphocyte critical to the innate immune system
NSCLC	Non-small-cell lung carcinoma
OX40	A member of the TNFR-superfamily of receptors which is not constitutively expressed on resting naïve T cells, unlike CD28. OX40 is a secondary costimulatory molecule, expressed after 24 to 72 hours following activation; its ligand, OX40L, is also not expressed on resting antigen presenting cells, but is following their activation. Expression of OX40 is dependent on full activation of the T cell
OS Benefit	Overall Survival benefit
PD1	Negatively regulate immune responses
PDL1	A protein that has been speculated to play a major role in suppressing the immune system during particular events such as pregnancy, tissue allografts, autoimmune disease and other disease states such as hepatitis
PFS	The length of time during and after medication or treatment during which the disease being treated does not get worse
Phagocytosis	The cellular process of engulfing solid particles by the cell membrane to form an internal phagosome by phagocytes and protists
T-cell	A group of white blood cells known as lymphocytes, and play a central role in cell-mediated immunity
TNFR	A tumour necrosis factor receptor (TNFR), or death receptor, is a trimeric cytokine receptor that binds tumour necrosis factors(TNF)
Tumour infiltrating Lymphocyte (TIL)	White blood cells that have left the bloodstream andmigrated into a tumour
Tyrosine Kinase inhibitors	A pharmaceutical drug that inhibits tyrosine kinases, an enzyme that can transfer a phosphate group from ATP to a protein in a cell. It functions as an "on" or "off" switch in many cellular functions
Unresectable	A tumour that cannot be removed completely through surgery

Source: Citi Research

Company Financials

Figure 36. Bristol Myers Squibb Annual Sales Model

$ mlns	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Cardiovascular											
Plavix	2,547	146	35	20	18	16	-	-	-	-	-
Avapro / Avalide	503	175	137	123	111	100	-	-	-	-	-
Eliquis (apixaban)	-	442	1,025	1,950	2,600	3,270	3,759	4,996	5,358	5,612	5,841
Other Cardiovascular	365	317	269	242	218	196	177	159	143	129	116
Total	**3,415**	**1,080**	**1,465**	**2,336**	**2,947**	**3,583**	**3,936**	**5,155**	**5,501**	**5,741**	**5,957**
Virology											
Reyataz	1,521	1,548	1,564	1,506	1,454	957	541	407	313	251	201
Sustiva Franchise	1,527	1,595	1,228	566	411	299	225	160	128	102	82
Baraclude	1,388	1,564	1,700	1,655	942	643	444	311	218	152	107
Other Virology	40	25	13	7	3	-	-	-	-	-	-
Total	**4,476**	**4,732**	**4,506**	**3,734**	**2,811**	**1,899**	**1,210**	**878**	**659**	**505**	**389**
Oncology											
Erbitux	702	697	686	667	650	631	505	-	-	-	-
Sprycel	1,019	1,182	1,324	1,407	1,434	1,414	1,400	1,414	1,419	652	351
Yervoy	706	1,016	1,270	1,442	1,569	1,600	1,632	1,665	1,698	1,732	1,767
Other Oncology	464	428	389	354	323	294	268	245	223	204	186
Total	**2,891**	**3,323**	**3,669**	**3,871**	**3,976**	**3,939**	**3,805**	**3,324**	**3,341**	**2,588**	**2,305**
Neuroscience											
Abilify	2,827	2,298	2,158	677	-	-	-	-	-	-	-
Other Neuroscience	19	12	7	5	3	-	-	-	-	-	-
Total	**2,846**	**2,310**	**2,165**	**682**	**3**	**-**	**-**	**-**	**-**	**-**	**-**
Immunioscience											
Orencia	1,176	1,434	1,678	1,929	2,149	2,350	2,439	2,552	2,591	2,641	2,701
Nulojix	11	40	67	102	119	137	151	166	183	201	221
Other Immunioscience	-	-	-	-	-	-	-	-	-	-	-
Total	**1,187**	**1,474**	**1,745**	**2,032**	**2,268**	**2,488**	**2,590**	**2,718**	**2,774**	**2,842**	**2,922**
Metabolics											
Onglyza/Kombiglyze	709	872	1,179	1,469	1,800	2,162	2,470	2,595	2,685	931	468
Byetta	149	355	280	252	227	204	184	165	149	134	120
Bydureon	78	262	325	422	507	583	670	771	886	975	1,072
Forxiga (dapagliflozin)	-	108	325	473	631	762	902	942	974	999	1,020
Other Metabolics	172	235	246	259	272	285	285	285	285	285	285
Total	**1,108**	**1,832**	**2,355**	**2,875**	**3,436**	**3,996**	**4,512**	**4,759**	**4,979**	**3,324**	**2,966**
Other Therapeutic Areas, Total	1,698	1,772	1,772	1,772	1,772	1,772	1,772	1,772	1,772	1,772	1,772
Pipeline											
Other Phase III Pipeline	-	-	-	911	2,277	3,642	4,945	6,265	7,421	8,296	8,851
Phase II Pipeline	-	-	-	-	499	1,343	2,144	2,863	3,358	3,902	4,412
Phase I Pipeline	-	-	-	-	-	-	91	228	594	822	913
Total Pipeline	**-**	**-**	**-**	**911**	**2,775**	**4,985**	**7,179**	**9,357**	**11,373**	**13,020**	**14,176**
Key Products	14,865	13,734	14,979	15,573	17,397	20,113	22,502	25,501	27,975	27,402	28,127
Mature Products and All Other	2,756	2,788	2,697	2,639	2,591	2,547	2,502	2,461	2,423	2,390	2,359
Total Pharmaceuticals Sales	**17,621**	**16,522**	**17,676**	**18,211**	**19,988**	**22,661**	**25,004**	**27,962**	**30,399**	**29,792**	**30,487**

Source: Company Data and Citi Research

Figure 37. Bristol Myers Squibb Annual Profit and Loss Account

$ mlns (except per share data)	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
GROUP											
Turnover	17,621	16,522	17,676	18,211	19,988	22,661	25,004	27,962	30,399	29,792	30,487
% Growth	-17.1%	-6.2%	7.0%	3.0%	9.8%	13.4%	10.3%	11.8%	8.7%	-2.0%	2.3%
% Growth (CER)	-15.1%	-6.2%	7.0%	3.0%	9.8%	13.4%	10.3%	11.8%	8.7%	-2.0%	2.3%
Non-GAAP COGS	(4,325)	(4,322)	(4,861)	(5,409)	(5,996)	(6,481)	(7,126)	(7,745)	(8,025)	(7,805)	(7,957)
% Sales	24.5%	26.2%	27.5%	29.7%	30.0%	28.6%	28.5%	27.7%	26.4%	26.2%	26.1%
% Growth	-21.7%	-0.1%	12.5%	11.3%	10.9%	8.1%	10.0%	8.7%	3.6%	-2.7%	1.9%
% Growth (CER)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Non-GAAP adjustment	(285)	(265)	(200)	(200)	(200)	(200)	(200)	(200)	(200)	(200)	(200)
COGS	(4,610)	(4,587)	(5,061)	(5,609)	(6,196)	(6,681)	(7,326)	(7,945)	(8,225)	(8,005)	(8,157)
% Sales	26.2%	27.8%	28.6%	30.8%	31.0%	29.5%	29.3%	28.4%	27.1%	26.9%	26.8%
Non-GAAP gross profit	13,296	12,200	12,815	12,803	13,992	16,180	17,878	20,216	22,374	21,986	22,530
Non-GAAP gross profit margin	75.5%	73.8%	72.5%	70.3%	70.0%	71.4%	71.5%	72.3%	73.6%	73.8%	73.9%
% Growth	-15.4%	-8.2%	5.0%	-0.1%	9.3%	15.6%	10.5%	13.1%	10.7%	-1.7%	2.5%
% Growth (CER)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Non-GAAP adjustment	(285)	(265)	(200)	(200)	(200)	(200)	(200)	(200)	(200)	(200)	(200)
Gross profit	13,011	11,935	12,615	12,603	13,792	15,980	17,678	20,016	22,174	21,786	22,330
Gross profit margin	73.8%	72.2%	71.4%	69.2%	69.0%	70.5%	70.7%	71.6%	72.9%	73.1%	73.2%
Non-GAAP SG&A	(4,932)	(5,039)	(4,486)	(4,600)	(4,946)	(5,193)	(5,297)	(5,403)	(5,511)	(5,621)	(5,734)
% Sales	28.0%	30.5%	25.4%	25.3%	24.7%	22.9%	21.2%	19.3%	18.1%	18.9%	18.8%
% Growth	-3.9%	2.2%	-11.0%	2.5%	7.5%	5.0%	2.0%	2.0%	2.0%	2.0%	2.0%
% Growth (CER)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Non-GAAP adjustment	(85)	(25)	(30)	(30)	(30)	(30)	(30)	(30)	(30)	(30)	(30)
SG&A	(5,017)	(5,064)	(4,516)	(4,630)	(4,976)	(5,223)	(5,327)	(5,433)	(5,541)	(5,651)	(5,764)
% Sales	28.5%	30.7%	25.5%	25.4%	24.9%	23.0%	21.3%	19.4%	18.2%	19.0%	18.9%
Non-GAAP R&D	(3,688)	(3,869)	(4,066)	(4,189)	(4,400)	(4,504)	(4,819)	(5,156)	(5,517)	(5,903)	(6,317)
% Sales	20.9%	23.4%	23.0%	23.0%	22.0%	19.9%	19.3%	18.4%	18.1%	19.8%	20.7%
% Growth	2.3%	4.9%	5.1%	3.0%	5.0%	2.4%	7.0%	7.0%	7.0%	7.0%	7.0%
% Growth (CER)	4.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Non-GAAP adjustment	(216)	(150)	(150)	(150)	(150)	(150)	(150)	(150)	(150)	(150)	(150)
R&D	(3,904)	(4,019)	(4,216)	(4,339)	(4,550)	(4,654)	(4,969)	(5,306)	(5,667)	(6,053)	(6,467)
% Sales	22.2%	24.3%	23.8%	23.8%	22.8%	20.5%	19.9%	19.0%	18.6%	20.3%	21.2%
Non-GAAP operating profit	**4,676**	**3,292**	**4,264**	**4,014**	**4,646**	**6,483**	**7,762**	**9,657**	**11,345**	**10,462**	**10,479**
Non-GAAP operating profit margin	26.5%	19.9%	24.1%	22.0%	23.2%	28.6%	31.0%	34.5%	37.3%	35.1%	34.4%
Margin expansion/(compression)	(635)bps	(661)bps	419 bps	(208)bps	120 bps	537 bps	243 bps	349 bps	279 bps	(221)bps	(74)bps
% Growth	-33.1%	-29.6%	29.5%	-5.9%	15.7%	39.5%	19.7%	24.4%	17.5%	-7.8%	0.2%
% Growth (CER)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Non-GAAP adjustment	(586)	(440)	(380)	(380)	(380)	(380)	(380)	(380)	(380)	(380)	(380)
Operating profit	**4,090**	**2,852**	**3,884**	**3,634**	**4,266**	**6,103**	**7,382**	**9,277**	**10,965**	**10,082**	**10,099**
Operating profit margin	**23.2%**	**17.3%**	**22.0%**	**20.0%**	**21.3%**	**26.9%**	**29.5%**	**33.2%**	**36.1%**	**33.8%**	**33.1%**
Interest payable	(182)	(210)	(246)	(269)	(282)	(297)	(305)	(305)	(310)	(317)	(320)
Interest income	106	64	57	63	68	77	87	98	111	127	142
Net finance costs	(76)	(146)	(189)	(205)	(214)	(220)	(218)	(207)	(198)	(190)	(179)
Non-GAAP net finance costs	(76)	(146)	(189)	(205)	(214)	(220)	(218)	(207)	(198)	(190)	(179)
Non-GAAP adjustment	-	-	-	-	-	-	-	-	-	-	-
Non-GAAP Other income/expense	299	282	400	450	450	450	450	450	450	450	450
Non-GAAP adjustment	(2,157)	(19)	-	-	-	-	-	-	-	-	-
Other income / expense	**(1,858)**	**263**	**400**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**
Non-GAAP share of after tax profits of associates & JVs	183	149	5	5	5	5	5	5	5	5	5
Non-GAAP adjustment	-	-	-	-	-	-	-	-	-	-	-
Share of after tax profits of associates & JVs	183	149	5	5	5	5	5	5	5	5	5

Source: Company Data and Citi Research

Figure 38. Bristol Myers Squibb Annual Profit & Loss Account

$ mlns (except per share data)	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Non-GAAP profit before tax	**5,082**	**3,577**	**4,480**	**4,264**	**4,887**	**6,718**	**7,999**	**9,904**	**11,602**	**10,727**	**10,756**
Non-GAAP profit before tax margin	28.8%	21.6%	25.3%	23.4%	24.4%	29.6%	32.0%	35.4%	38.2%	36.0%	35.3%
% Growth	-31.6%	-29.6%	25.2%	-4.8%	14.6%	37.5%	19.1%	23.8%	17.1%	-7.5%	0.3%
% Growth (CER)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Non-GAAP adjustment	(2,743)	(459)	(380)	(380)	(380)	(380)	(380)	(380)	(380)	(380)	(380)
Profit before tax	**2,339**	**3,118**	**4,100**	**3,884**	**4,507**	**6,338**	**7,619**	**9,524**	**11,222**	**10,347**	**10,376**
Profit before tax margin	13.3%	18.9%	23.2%	21.3%	22.5%	28.0%	30.5%	34.1%	36.9%	34.7%	34.0%
Non-GAAP tax	(1,178)	(547)	(687)	(746)	(855)	(1,176)	(1,400)	(1,733)	(2,030)	(1,877)	(1,882)
Non-GAAP effective tax rate	23.2%	15.3%	15.3%	17.5%	17.5%	17.5%	17.5%	17.5%	17.5%	17.5%	17.5%
% Growth	-39.7%	-53.6%	25.6%	8.5%	14.6%	37.5%	19.1%	23.8%	17.1%	-7.5%	0.3%
Non-GAAP adjustment	(1,339)	(70)	(150)	(150)	(150)	(150)	(175)	(175)	(175)	(175)	(175)
Tax	161	(477)	(537)	(596)	(705)	(1,026)	(1,225)	(1,558)	(1,855)	(1,702)	(1,707)
Effective tax rate	-6.9%	15.3%	13.1%	15.3%	15.6%	16.2%	16.1%	16.4%	16.5%	16.5%	16.5%
Non-GAAP profit after tax	**3,904**	**3,030**	**3,793**	**3,517**	**4,032**	**5,542**	**6,599**	**8,171**	**9,572**	**8,850**	**8,874**
Non-GAAP profit after tax margin	29.4%	24.8%	29.6%	27.5%	28.8%	34.3%	36.9%	40.4%	42.8%	40.3%	39.4%
% Growth	-28.7%	-22.4%	25.2%	-7.3%	14.6%	37.5%	19.1%	23.8%	17.1%	-7.5%	0.3%
% Growth (CER)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Non-GAAP adjustment	(1,404)	(389)	(230)	(230)	(230)	(230)	(205)	(205)	(205)	(205)	(205)
Profit after tax	**2,500**	**2,641**	**3,563**	**3,287**	**3,802**	**5,312**	**6,394**	**7,966**	**9,367**	**8,645**	**8,669**
Profit after tax margin	14.2%	16.0%	20.2%	18.1%	19.0%	23.4%	25.6%	28.5%	30.8%	29.0%	28.4%
Profit attributable to non-controlling interests	(541)	(12)	(16)	(15)	(18)	(25)	(30)	(38)	(45)	(42)	(42)
Non-GAAP profit attributable to shareholders	3,363	3,018	3,777	3,502	4,014	5,517	6,569	8,133	9,527	8,808	8,832
% Growth	-14.2%	-10.3%	25.1%	-7.3%	14.6%	37.4%	19.1%	23.8%	17.1%	-7.5%	0.3%
% Growth (CER)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Non-GAAP adjustment	(1,404)	(389)	(230)	(230)	(230)	(230)	(205)	(205)	(205)	(205)	(205)
Net Earnings	**1,959**	**2,629**	**3,547**	**3,272**	**3,784**	**5,287**	**6,364**	**7,928**	**9,322**	**8,603**	**8,627**
Discontinued operations' profit/ (loss)	-	-	-	-	-	-	-	-	-	-	-
Net Earnings post discontinued operations	1,959	2,629	3,547	3,272	3,784	5,287	6,364	7,928	9,322	8,603	8,627
Earnings attributable to unvested restricted shares	(1)	-	-	-	-	-	-				
Profit attributable to shareholders	**1,958**	**2,629**	**3,547**	**3,272**	**3,784**	**5,287**	**6,364**	**7,928**	**9,322**	**8,603**	**8,627**
Shares Outstanding (basic)	1,670	1,632	1,628	1,630	1,632	1,631	1,628	1,622	1,613	1,604	1,598
Shares Outstanding (diluted)	1,688	1,650	1,646	1,648	1,650	1,649	1,646	1,640	1,631	1,622	1,616
Non-GAAP EPS (basic)	**2.01**	**1.85**	**2.32**	**2.15**	**2.46**	**3.38**	**4.03**	**5.01**	**5.91**	**5.49**	**5.53**
% Growth	-12.7%	-8.2%	25.5%	-7.4%	14.5%	37.5%	19.3%	24.3%	17.8%	-7.0%	0.7%
Non-GAAP EPS (diluted)	**1.99**	**1.83**	**2.29**	**2.13**	**2.43**	**3.35**	**3.99**	**4.96**	**5.84**	**5.43**	**5.47**
% Growth	-12.8%	-8.2%	25.5%	-7.4%	14.5%	37.5%	19.3%	24.3%	17.8%	-7.0%	0.7%
EPS (basic)	**1.17**	**1.61**	**2.18**	**2.01**	**2.32**	**3.24**	**3.91**	**4.89**	**5.78**	**5.36**	**5.40**
% Growth	-46.1%	37.4%	35.3%	-7.9%	15.5%	39.8%	20.6%	25.0%	18.2%	-7.2%	0.7%
EPS (diluted)	**1.16**	**1.59**	**2.16**	**1.99**	**2.29**	**3.21**	**3.87**	**4.83**	**5.71**	**5.30**	**5.34**
% Growth	-46.2%	37.4%	35.2%	-7.9%	15.5%	39.8%	20.6%	25.0%	18.2%	-7.2%	0.7%
DPS	**1.37**	**1.41**	**1.44**	**1.55**	**1.60**	**1.69**	**2.02**	**2.51**	**2.96**	**2.75**	**2.77**
% Growth	3.0%	3.0%	2.0%	7.4%	3.4%	5.9%	19.4%	24.4%	17.9%	-7.1%	0.6%

Source: Company Data and Citi Research

Figure 39. Bristol Myers Squibb Pipeline

Product	Preclin.	I	II	III	Filed	Year	Peak Sales	Risk Adj Peak Sales	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Cardiovascular							**3,550**	**781**	**-**	**-**	**-**	**-**	**78**	**195**	**312**	**424**	**537**	**637**
LXR Modulators						2017	1,000	220	-	-	-	-	22	55	88	119	151	179
PCSK9 Adnectin						2017	1,000	220	-	-	-	-	22	55	88	119	151	179
CCR2 / 5 Antagonists						2017	750	165	-	-	-	-	17	41	66	90	114	134
Factor Xla Parental						2017	200	44	-	-	-	-	4	11	18	24	30	36
Factor Xla Oral						2017	200	44	-	-	-	-	4	11	18	24	30	36
IKur Antagonists						2017	200	44	-	-	-	-	4	11	18	24	30	36
PEG-Relaxin						2017	200	44	-	-	-	-	4	11	18	24	30	36
Virology							**2,750**	**1,085**	**-**	**-**	**81**	**230**	**393**	**550**	**707**	**849**	**962**	**1,038**
Daclatasvir (NS5A inhibitor)						2015	1,000	540	-	-	54	135	216	293	372	440	492	525
Asunaprevir (NS3 Inhibitor)						2015	250	135	-	-	14	34	54	73	93	110	123	131
Peginterferon lambda-1a						2015	250	135	-	-	14	34	54	73	93	110	123	131
HIV Attachment Inhibitor						2016	250	55	-	-	-	6	14	22	30	38	45	50
NRT Inhibitor						2016	200	44	-	-	-	4	11	18	24	30	36	40
HIV Maturation Inhibitor						2016	200	44	-	-	-	4	11	18	24	30	36	40
NS5B Primer Grip Inhibitor						2016	200	44	-	-	-	4	11	18	24	30	36	40
NSSB Non Nuc						2016	200	44	-	-	-	4	11	18	24	30	36	40
NS5B Site 1 Inhibitor						2016	200	44	-	-	-	4	11	18	24	30	36	40
Oncology							**20,550**	**11,725**	**-**	**-**	**819**	**2,401**	**4,159**	**5,861**	**7,554**	**9,107**	**10,342**	**11,181**
Brivanib						2015	200	108	-	-	11	27	43	59	74	88	98	105
Elotuzumab						2015	2,000	1,080	-	-	108	270	432	586	743	880	984	1,050
Necitumumab						2015		-	-	-	-	-	-	-	-	-	-	-
Anti-Fucosyl GM1						2016	200	44	-	-	-	4	11	18	24	30	36	40
JAK2 Inhibitor						2016	1,000	220	-	-	-	22	55	88	119	151	179	200
IL-21						2016	200	44	-	-	-	4	11	18	24	30	36	40
Anti-KIR (lirilumab)						2016	3,000	1,050	-	-	-	105	263	420	570	722	856	957
Urelumab (Anti-CD137)						2016	3,000	1,050	-	-	-	105	263	420	570	722	856	957
Notch Inhibitors						2016	200	44	-	-	-	4	11	18	24	30	36	40
Anti-PD1 (nivolumab)						2015	7,000	7,000	-	-	700	1,750	2,800	3,801	4,816	5,705	6,377	6,804
Anti-PD-L1						2016	1,000	220	-	-	-	22	55	88	119	151	179	200
Anti-CXCR4						2016	750	165	-	-	-	17	41	66	90	114	134	150
Anti-LAG3						2016	2,000	700	-	-	-	70	175	280	380	482	571	638
Neuroscience							**2,350**	**517**	**-**	**-**	**-**	**52**	**129**	**207**	**281**	**356**	**421**	**471**
α-7 Nicotinic Agonist						2016	200	44	-	-	-	4	11	18	24	30	36	40
Triple Reuptake Inhibitors						2016	200	44	-	-	-	4	11	18	24	30	36	40
Microtubule Stabilizer						2016	750	165	-	-	-	17	41	66	90	114	134	150
Avagacestat (Gamma Secretase Inhibitor)						2016	1,000	220	-	-	-	22	55	88	119	151	179	200
Myostatin Adnectin						2016	200	44	-	-	-	4	11	18	24	30	36	40

Source: Company Data and Citi Research

Figure 40. Bristol Myers Squibb Pipeline continued

Product	Preclin.	I	II	III	Filed	Year	Peak Sales	Risk Adj Peak Sales	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Immunioscience							**3,000**	**660**	**-**	**-**	**-**	**66**	**165**	**264**	**358**	**454**	**538**	**601**
CCR1 Antagonists						2016	300	66	-	-	-	7	17	26	36	45	54	60
Anti-IP10						2016	300	66	-	-	-	7	17	26	36	45	54	60
Anti-CD28						2016	300	66	-	-	-	7	17	26	36	45	54	60
Anti-IL6 (clazakizumab)						2016	300	66	-	-	-	7	17	26	36	45	54	60
Anti-CD40						2016	300	66	-	-	-	7	17	26	36	45	54	60
IL-17/IL-23 biAb						2016	300	66	-	-	-	7	17	26	36	45	54	60
Anti-IL31						2016	300	66	-	-	-	7	17	26	36	45	54	60
Anti-CD40L						2016	300	66	-	-	-	7	17	26	36	45	54	60
LPA1 Antagonist						2016	300	66	-	-	-	7	17	26	36	45	54	60
S1P1 modulator						2016	300	66	-	-	-	7	17	26	36	45	54	60
Metabolics							**1,000**	**284**	**-**	**-**	**11**	**27**	**61**	**103**	**145**	**184**	**219**	**248**
PEG-FGF21						2017	200	44	-	-	-	-	4	11	18	24	30	36
11βHSD Inhibitors						2017	200	44	-	-	-	-	4	11	18	24	30	36
GPR119 Agonist						2017	200	44	-	-	-	-	4	11	18	24	30	36
GPR40 Agonist						2017	200	44	-	-	-	-	4	11	18	24	30	36
metreleptin						2015	200	108	-	-	11	27	43	59	74	88	98	105
TOTAL ($)							**33,200**	**15,052**	**-**	**-**	**911**	**2,775**	**4,985**	**7,179**	**9,357**	**11,373**	**13,020**	**14,176**

Source: Company Data and Citi Research

Figure 41. Bristol Myers Squibb Annual Balance Sheet

$ mlns	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
ASSETS											
Current assets											
Cash and cash equivalents	1,656	1,806	2,528	2,781	3,213	4,600	5,576	6,892	9,072	11,507	13,399
Marketable securities	1,173	1,173	1,173	1,173	1,173	1,173	1,173	1,173	1,173	1,173	1,173
Trade receivables	3,083	3,200	3,424	3,527	3,872	4,389	4,843	5,416	5,888	5,770	5,905
Inventories	1,657	1,519	1,709	1,902	2,108	2,278	2,505	2,723	2,821	2,744	2,797
Deferred Income taxes	1,597	1,597	1,597	1,597	1,597	1,597	1,597	1,597	1,597	1,597	1,597
Prepaid expenses and others	355	333	356	367	403	457	504	563	612	600	614
Assets held for sale	-	-	-	-	-	-	-	-	-	-	-
Total current assets	**9,521**	**9,628**	**10,786**	**11,347**	**12,365**	**14,494**	**16,198**	**18,364**	**21,164**	**23,392**	**25,485**
Non-current assets											
Property, plant and equipment	5,333	5,450	5,579	5,720	5,873	6,040	6,220	6,415	6,624	6,848	7,089
Goodwill	7,635	7,635	7,635	7,635	7,635	7,635	7,635	7,635	7,635	7,635	7,635
Other intangible assets	8,778	8,814	8,867	8,934	9,014	9,107	9,211	9,326	9,452	9,587	9,733
Deferred income taxes	203	203	203	203	203	203	203	203	203	203	203
Marketable securities	3,523	3,523	3,523	3,523	3,523	3,523	3,523	3,523	3,523	3,523	3,523
Other non-current assets	904	904	904	904	904	904	904	904	904	904	904
Total non-current assets	**26,376**	**26,530**	**26,711**	**26,919**	**27,153**	**27,412**	**27,696**	**28,006**	**28,341**	**28,701**	**29,087**
TOTAL ASSETS	**35,897**	**36,158**	**37,497**	**38,266**	**39,518**	**41,906**	**43,894**	**46,370**	**49,505**	**52,093**	**54,573**
LIABILITIES											
Current liabilities											
Short-term borrowings	826	826	826	826	826	826	826	826	826	826	826
Accounts payable	2,202	2,455	2,489	2,635	2,847	3,003	3,200	3,397	3,536	3,588	3,713
Accrued expenses	2,573	2,597	2,316	2,375	2,552	2,679	2,732	2,786	2,842	2,898	2,956
Deferred income	825	833	743	761	818	859	876	893	911	929	948
Accrued rebates and returns	1,054	554	554	554	554	554	554	554	554	554	554
Other payables	-	-	-	-	-	-	-	-	-	-	-
U.S. and foreign income taxes payable	193	193	193	193	193	193	193	193	193	193	193
Dividends payable	606	612	545	559	601	631	643	656	669	683	696
Total current liabilities	**8,279**	**8,070**	**7,667**	**7,903**	**8,392**	**8,744**	**9,025**	**9,306**	**9,531**	**9,671**	**9,886**
Non-current liabilities											
Pensions and other post-employment benefits	1,882	1,882	1,882	1,882	1,882	1,882	1,882	1,882	1,882	1,882	1,882
Deferred income	4,024	4,024	4,024	4,024	4,024	4,024	4,024	4,024	4,024	4,024	4,024
U.S. and foreign income taxes payable	648	680	714	750	788	827	868	912	957	1,005	1,056
Other non-current liabilities	858	858	858	858	858	858	858	858	858	858	858
Long-term borrowings	6,568	7,885	9,135	9,726	10,226	10,894	10,894	10,894	11,235	11,485	11,485
Total non-current liabilities	**13,980**	**15,329**	**16,613**	**17,240**	**17,778**	**18,485**	**18,526**	**18,570**	**18,956**	**19,254**	**19,305**
TOTAL LIABILITIES	**22,259**	**23,399**	**24,280**	**25,143**	**26,169**	**27,229**	**27,551**	**27,876**	**28,488**	**28,925**	**29,191**
NET ASSETS	**13,638**	**12,758**	**13,217**	**13,123**	**13,349**	**14,677**	**16,344**	**18,494**	**21,017**	**23,168**	**25,382**
EQUITY											
Share capital	221	221	221	221	221	221	221	221	221	221	221
Capital in excess of par value of stock	2,694	2,694	2,694	2,694	2,694	2,694	2,694	2,694	2,694	2,694	2,694
Accumulated other comprehensive loss	(3,202)	(3,202)	(3,202)	(3,202)	(3,202)	(3,202)	(3,202)	(3,202)	(3,202)	(3,202)	(3,202)
Retained earnings	32,733	31,853	32,312	32,218	32,444	33,772	35,439	37,589	40,112	42,263	44,477
Less cost of treasury stock	(18,823)	(18,823)	(18,823)	(18,823)	(18,823)	(18,823)	(18,823)	(18,823)	(18,823)	(18,823)	(18,823)
	13,623	**12,743**	**13,202**	**13,108**	**13,334**	**14,662**	**16,329**	**18,479**	**21,002**	**23,153**	**25,367**
Noncontrolling interest	15	15	15	15	15	15	15	15	15	15	15
TOTAL EQUITY	**13,638**	**12,758**	**13,217**	**13,123**	**13,349**	**14,677**	**16,344**	**18,494**	**21,017**	**23,168**	**25,382**
Net Debt (inc pension)	6,447	7,614	8,142	8,480	8,548	7,829	6,853	5,537	3,698	1,513	(379)
Net Debt (exc pension)	4,565	5,732	6,260	6,598	6,666	5,947	4,971	3,655	1,816	(369)	(2,261)

Source: Company Data and Citi Research

Figure 42. Bristol Myers Squibb Annual Cashflow Statement

$ mlns	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Cash flows from operating activities											
Net profit profit - as in reported cash flow	**2,500**	**2,641**	**3,563**	**3,287**	**3,802**	**5,312**	**6,394**	**7,966**	**9,367**	**8,645**	**8,669**
Net earnings attributable to noncontrolling interest	(541)										
Depreciation	382	295	309	324	340	356	374	392	412	432	454
Amortisation	607	626	636	649	665	682	702	723	746	771	797
Deferred income tax expense	(1,230)	-	-	-	-	-	-	-	-	-	-
Stock-based compensation expense	154										
Impairment charges	2,180	-	-	-	-	-	-	-	-	-	-
Gain related to divestitures of discontinued operations	-										
Acquired in-process research and development	-										
Gain on sale of ImClone shares	-										
Profit/Loss on sale of tangible fixed assets											
Other adjustments	3,228	-	-	-	-	-	-	-	-	-	-
Changes in operating assets and liabilities:											
Receivables	648	(95)	(247)	(114)	(380)	(571)	(501)	(632)	(521)	130	(149)
Inventories	(103)	138	(190)	(193)	(207)	(170)	(227)	(218)	(98)	77	(53)
Accounts payable	(232)	291	(403)	237	489	352	280	282	225	139	215
Deferred income	295										
U.S. and foreign income taxes payable	(50)	32	34	36	38	39	41	43	46	48	50
Other	(897)	(500)	-	-	-	-	-	-	-	-	-
Cash generated from operations	**6,941**	**3,428**	**3,702**	**4,226**	**4,746**	**6,000**	**7,063**	**8,557**	**10,176**	**10,242**	**9,984**
Taxation paid											
Net cash inflow from operating activities	**6,941**	**3,428**	**3,702**	**4,226**	**4,746**	**6,000**	**7,063**	**8,557**	**10,176**	**10,242**	**9,984**
Cash flow from investing activities											
Proceeds from sale and maturities of marketable securities	4,890										
Purchases of marketable securities	(3,607)	-	-	-	-	-	-	-	-	-	-
Additions to property, plant and equipment and capitalized software	(548)	(412)	(438)	(465)	(493)	(523)	(554)	(587)	(621)	(657)	(695)
Proceeds from sale of businesses and other investing activities	68										
Mead Johnson's cash at split-off	-										
Purchase of businesses, net of cash acquired	(7,530)										
Proceeds from divestitures of discontinued operations											
Proceeds from sale of ImClone shares											
Proceeds from sale and leaseback of properties											
Proceeds from sale of tangible fixed assets		-	-	-	-	-	-	-	-	-	-
Purchase of intangible assets		(662)	(689)	(716)	(745)	(775)	(806)	(838)	(872)	(907)	(943)
Investment in joint ventures and associated undertakings	-										
Interest received	-										
Dividends from joint ventures and associated undertakings / Other	-										
Net cash outflow from investing activities	**(6,727)**	**(1,075)**	**(1,127)**	**(1,181)**	**(1,238)**	**(1,298)**	**(1,360)**	**(1,425)**	**(1,493)**	**(1,564)**	**(1,638)**
Cash flow from financing activities											
Short-term debt repayments	49	-	-	-	-	-	-	-	-	-	-
Long-term debt borrowings	1,950	1,250	1,250	1,250	1,250	1,250	-	-	1,000	1,000	-
Long-term debt repayments	(2,108)	67	-	(659)	(750)	(582)	-	-	(659)	(750)	-
Common stock repurchases	(2,403)	(1,200)	(740)	(845)	(949)	(1,200)	(1,413)	(1,711)	(2,035)	(2,048)	(1,997)
Dividends paid	(2,286)	(2,309)	(2,347)	(2,522)	(2,609)	(2,758)	(3,284)	(4,066)	(4,763)	(4,404)	(4,416)
Proceeds from Mead Johnson initial public offering	-										
Interest paid	-										
Dividends paid to minority interests	-	(12)	(16)	(15)	(18)	(25)	(30)	(38)	(45)	(42)	(42)
Net cash outflow from financing activities	**(4,333)**	**(2,204)**	**(1,854)**	**(2,791)**	**(3,076)**	**(3,316)**	**(4,727)**	**(5,816)**	**(6,503)**	**(6,244)**	**(6,454)**
Increase/(Decrease) in Cash and Cash Equivalents	**(4,120)**	**150**	**722**	**254**	**431**	**1,387**	**976**	**1,316**	**2,181**	**2,435**	**1,892**
Cash and Cash Equivalents at Beginning of Year	**5,776**	**1,656**	**1,806**	**2,528**	**2,781**	**3,213**	**4,600**	**5,576**	**6,892**	**9,072**	**11,507**
Cash and Cash Equivalents at End of Year	**1,656**	**1,806**	**2,528**	**2,781**	**3,213**	**4,600**	**5,576**	**6,892**	**9,072**	**11,507**	**13,399**
Cash and cash equivalents (balance sheet)	**1,656**	**1,806**	**2,528**	**2,781**	**3,213**	**4,600**	**5,576**	**6,892**	**9,072**	**11,507**	**13,399**

Source: Company Data and Citi Research

Figure 43. Roche Annual Sales Model

SFr mlns	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Oncology											
Mabthera / Rituxan	6,707	7,017	7,368	7,696	7,686	7,262	6,791	5,960	5,348	4,823	4,373
Herceptin	5,889	5,964	6,795	6,854	6,665	6,214	5,732	4,964	4,241	3,625	3,099
Xeloda	1,523	1,438	787	563	427	325	252	204	181	163	149
Kytril	86	76	69	62	56	50	45	41	37	33	30
Tarceva	1,276	1,334	1,361	1,397	1,430	1,473	1,512	637	554	505	481
Avastin	5,764	6,267	6,645	6,978	7,180	7,359	7,541	6,946	6,269	5,737	4,618
Zelboraf	234	456	480	343	105	107	110	112	115	115	115
Perjeta	56	753	1,390	1,737	1,853	3,135	3,930	4,673	5,626	5,626	5,626
Erivedge	29	84	134	175	210	241	265	292	306	322	338
Total	**21,564**	**23,389**	**25,030**	**25,804**	**25,612**	**26,167**	**26,179**	**23,829**	**22,678**	**20,949**	**18,828**
Virology											
Pegasys	1,649	1,442	1,356	1,016	749	593	475	411	361	319	286
Copegus	101	75	56	51	45	41	37	33	30	27	24
Viracept	-	-	-	-	-	-	-	-	-	-	-
Cymevene / Valcyte	638	672	707	495	524	419	336	268	215	172	137
Fuzeon	148	139	111	89	89	89	89	71	57	45	36
Total	**2,536**	**2,328**	**2,230**	**1,649**	**1,408**	**1,142**	**937**	**783**	**662**	**564**	**484**
Blood / Metabolism											
NeoRecormon	674	560	490	428	375	328	288	252	221	194	171
Cellcept	909	859	759	658	573	499	437	383	337	296	262
Neutrogin	261	244	232	221	210	199	189	180	171	162	154
Xenical	184	172	155	140	126	113	73	26	10	4	2
Nutropin / Protropin	304	252	202	161	129	103	83	66	53	42	34
Bonviva	323	159	96	77	61	49	39	31	25	20	16
Mircera	384	394	502	651	820	904	940	968	997	1,027	1,058
Total	**3,039**	**2,641**	**2,435**	**2,336**	**2,293**	**2,196**	**2,049**	**1,906**	**1,814**	**1,746**	**1,695**
Cardiology / Respiratory											
Dilatrend	133	118	106	96	86	77	70	63	56	51	46
Pulmozyme	537	555	500	450	405	364	328	295	266	239	215
Activase / TNKase	584	641	609	579	550	522	496	471	448	425	404
Xolair	705	750	803	859	902	902	767	652	554	471	400
Tamiflu	560	631	600	570	558	391	274	246	222	199	180
Total	**2,519**	**2,695**	**2,618**	**2,553**	**2,501**	**2,257**	**1,934**	**1,727**	**1,545**	**1,386**	**1,245**
Other											
Rocephin	266	249	236	225	213	203	193	183	174	165	157
Madopar	310	316	323	329	336	343	349	356	364	371	378
Roaccutane	81	78	74	71	67	64	61	58	55	52	49
Lucentis	1,481	1,560	1,560	1,638	1,719	1,805	1,896	1,991	2,090	2,195	2,304
Lexotan	-	-	-	-	-	-	-	-	-	-	-
Actemra	842	1,098	1,356	1,619	1,869	2,018	2,122	2,194	2,269	2,337	2,407
Total	**2,980**	**3,301**	**3,549**	**3,881**	**4,205**	**4,433**	**4,620**	**4,781**	**4,951**	**5,119**	**5,295**
Other Pharma	2,594	2,464	2,466	2,466	2,466	2,466	2,466	2,466	2,466	2,466	2,466
New Products	-	441	1,738	2,962	5,429	9,117	13,341	18,708	22,976	26,595	28,053
Phase I & Other	-	-	-	-	183	457	1,187	1,644	1,827	-	-
EU HC reform impact	-	(200)	(207)	(212)	(223)	(226)	(234)	(253)	(267)	(280)	(268)
Pharmaceuticals	**35,232**	**37,058**	**39,860**	**41,439**	**43,690**	**47,553**	**51,291**	**53,949**	**56,825**	**58,544**	**57,799**
Growth (reported)	7.4%	5.2%	7.6%	4.0%	5.4%	8.8%	7.9%	5.2%	5.3%	3.0%	-1.3%
Diabetes Care	2,566	2,091	1,902	1,731	1,645	1,645	1,645	1,645	1,645	1,645	1,645
Professional Diagnostics	5,165	5,485	5,897	6,339	6,814	7,325	7,875	8,465	9,100	9,783	10,517
Molecular Diagnostics	1,168	1,185	1,233	1,282	1,334	1,387	1,442	1,500	1,560	1,622	1,687
Applied Science	737	691	691	712	733	755	778	801	825	850	876
Ventana (Tissue Diagnostics)	631	685	739	784	823	864	907	953	1,000	1,050	1,103
Diagnostics	**10,267**	**10,137**	**10,463**	**10,848**	**11,349**	**11,977**	**12,647**	**13,364**	**14,131**	**14,951**	**15,827**
Growth (reported)	5.4%	-1.3%	3.2%	3.7%	4.6%	5.5%	5.6%	5.7%	5.7%	5.8%	5.9%
Total Sales	**45,499**	**47,196**	**50,322**	**52,288**	**55,039**	**59,529**	**63,938**	**67,313**	**70,956**	**73,494**	**73,626**
Growth (reported)	7.0%	3.7%	6.6%	3.9%	5.3%	8.2%	7.4%	5.3%	5.4%	3.6%	0.2%

Source: Company Data and Citi Research

Figure 44. Roche Pipeline

Product/Indication	Preclin.	I	II	III	Filed	Peak Sales (SFr mm)	Risk-adjusted Peak Sales	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Inflammation/Bone							**2,390**	**-**	**-**	**-**	**135**	**523**	**878**	**1,223**	**1,569**	**1,884**	**2,122**
Ocrelizumab (RG1594)						2,000	1,080	-	-	-	108	270	432	583	745	886	983
Quilizumab (RG7449)						500	110	-	-	-	-	11	28	44	59	76	90
Lebrikizumab/Anti-IL13 (RG3637)						500	270	-	-	-	27	68	108	146	186	221	246
Rontalizumab/Anti-IFNá (RG7415)						1,500	330	-	-	-	-	33	83	132	178	228	271
Anti-LT alpha (RG7416)						500	110	-	-	-	-	11	28	44	59	76	90
RG7413						1,000	220	-	-	-	-	22	55	88	119	152	180
GRG3806						500	270					108	146	186	221	246	262
Metabolism							**2,544**	**-**	**5**	**14**	**238**	**591**	**967**	**1,326**	**1,702**	**2,035**	**2,276**
R1439 (aleglitazar)						4,000	2,160	-	-	-	216	540	864	1,166	1,490	1,771	1,966
Tofogliflozin (CHU)						100	54	-	5	14	22	29	37	44	49	52	54
P-selectin huMAb (RG1512)						500	110	-	-	-	-	-	11	28	44	59	76
RG7652						1,000	220	-	-	-	-	22	55	88	119	152	180
Oncology							**18,805**	**441**	**1,732**	**2,829**	**4,732**	**7,340**	**10,295**	**14,338**	**17,297**	**19,736**	**20,239**
RG7159 (GA101) - obinutuzumab						4,000	3,320	-	332	830	1,328	1,793	2,291	2,722	3,021	3,220	3,320
R3502 (T-DM1)						6,630	6,630	441	1,400	1,918	2,701	3,742	4,628	6,276	6,630	6,630	6,630
RG3638 MetMab - onartuzumab						1,500	810	-	-	81	203	324	437	559	664	737	786
RG7414						500	110	-	-	-	-	11	28	44	59	76	90
huMAb EGFR/GA201 (RG7160)						2,000	440	-	-	-	-	44	110	176	238	304	361
RG7321						2,000	440	-	-	-	-	-	44	110	176	238	304
RG7422						500	110	-	-	-	-	-	11	28	44	59	76
Immunoconjugates						5,000	1,100	-	-	-	110	275	440	594	759	902	1,001
RG7593						500	110	-	-	-	-	-	11	28	44	59	76
RG7596						500	110	-	-	-	-	-	11	28	44	59	76
RG7597						500	110	-	-	-	-	-	11	28	44	59	76
RG7686						500	110	-	-	-	-	-	11	28	44	59	76
RG7421+RG7204						750	405	-	-	-	41	101	162	219	279	332	369
RG7446 (MPDL3280A)						9,000	5,000	-	-	-	350	1,050	2,100	3,500	5,250	7,000	7,000
Virology							**660**	**-**	**-**	**-**	**-**	**66**	**165**	**264**	**356**	**455**	**541**
RG7128 (mericitabine)						750	165	-	-	-	-	17	41	66	89	114	135
RG7227 (danoprevir)						750	165	-	-	-	-	17	41	66	89	114	135
RG7790 (setrobuvir)						750	165	-	-	-	-	17	41	66	89	114	135
RG7667						750	165	-	-	-	-	17	41	66	89	114	135
CNS							**2,956**	**-**	**-**	**119**	**325**	**544**	**900**	**1,341**	**1,761**	**2,112**	**2,432**
bitopertin (R1678)						2,000	1,080	-	-	108	270	432	583	745	886	983	1,048
SST (arbaclofen)						500	270	-	-	-	27	68	108	146	186	221	246
RG7090						500	110	-	-	11	28	44	59	76	90	100	107
crenezumab (RG7412)						2,000	440	-	-	-	-	-	44	110	176	238	304
Gantenerumab/Anti-Aâ (RG1450)						3,000	660	-	-	-	-	-	66	165	264	356	455
RG1577						300	66	-	-	-	-	-	7	17	26	36	46
RG1578						500	110	-	-	-	-	-	11	28	44	59	76
RG1594						1,000	220				-	-	22	55	88	119	152
Opthalmology							**540**	**-**	**-**	**-**	**-**	**54**	**135**	**216**	**292**	**373**	**443**
Anti-Factor D (RG7417)						1,000	540	-	-	-	-	54	135	216	292	373	443
TOTAL (SFr)							**27,895**	**441**	**1,738**	**2,962**	**5,429**	**9,117**	**13,341**	**18,708**	**22,976**	**26,595**	**28,053**

Source: Citi Research

Figure 45. Roche Annual Profit and Loss

SFr mlns	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Sales	**45,499**	**47,196**	**50,322**	**52,288**	**55,039**	**59,529**	**63,938**	**67,313**	**70,956**	**73,494**	**73,626**
Royalties and other operating income	1,945	1,731	1,736	1,742	1,749	1,758	1,768	1,177	1,188	1,200	1,213
Cost of sales	(12,175)	(12,044)	(12,330)	(12,580)	(12,762)	(13,306)	(13,890)	(14,234)	(14,650)	(15,188)	(15,460)
Marketing and distribution	(8,539)	(8,883)	(9,442)	(9,698)	(10,086)	(10,625)	(11,038)	(11,215)	(11,394)	(11,811)	(11,286)
Research and development	(9,552)	(9,703)	(10,391)	(10,798)	(11,372)	(11,861)	(12,507)	(12,617)	(13,290)	(13,433)	(13,359)
General and Administration	(3,053)	(1,982)	(2,005)	(2,079)	(2,182)	(2,347)	(2,510)	(2,638)	(2,775)	(2,875)	(2,891)
Operating profit	**14,125**	**16,314**	**17,889**	**18,875**	**20,386**	**23,148**	**25,761**	**27,786**	**30,034**	**31,388**	**31,843**
% margin	31.0%	34.6%	35.5%	36.1%	37.0%	38.9%	40.3%	41.3%	42.3%	42.7%	43.2%
Income from associated companies	-	-	-	-	-	-	-	-	-	-	-
Financial income/(expense)	(1,802)	(1,678)	(1,113)	(725)	(330)	(323)	(299)	(268)	(237)	(208)	(181)
Exceptional financial items	-	-	-	-	-	-	-	-	-	-	-
Profit before taxes	**12,323**	**14,636**	**16,776**	**18,150**	**20,055**	**22,824**	**25,461**	**27,517**	**29,797**	**31,180**	**31,662**
% margin	27.1%	31.0%	33.3%	34.7%	36.4%	38.3%	39.8%	40.9%	42.0%	42.4%	43.0%
Income taxes	(2,550)	(3,074)	(3,523)	(3,811)	(4,212)	(4,793)	(5,347)	(5,779)	(6,257)	(6,548)	(6,649)
% tax rate	20.7%	21.0%	21.0%	21.0%	21.0%	21.0%	21.0%	21.0%	21.0%	21.0%	21.0%
Profit from continuing businesses	**9,773**	**11,563**	**13,253**	**14,338**	**15,844**	**18,031**	**20,115**	**21,739**	**23,540**	**24,632**	**25,013**
% margin	21.5%	24.5%	26.3%	27.4%	28.8%	30.3%	31.5%	32.3%	33.2%	33.5%	34.0%
Profit from discontinued businesses	-	-	-	-	-	-	-	-	-	-	-
Net income	**9,773**	**11,563**	**13,253**	**14,338**	**15,844**	**18,031**	**20,115**	**21,739**	**23,540**	**24,632**	**25,013**
Minority interests	(234)	(334)	(347)	(359)	(371)	(384)	(397)	(410)	(424)	(438)	(453)
Net income attributable to Roche shareholders	**9,539**	**11,229**	**12,906**	**13,980**	**15,473**	**17,647**	**19,718**	**21,328**	**23,116**	**24,194**	**24,560**
% margin	21.0%	23.8%	25.6%	26.7%	28.1%	29.6%	30.8%	31.7%	32.6%	32.9%	33.4%
Diluted shares	855	854	854	854	854	854	854	854	854	854	854
Diluted Net Income	9,539	11,229	12,906	13,980	15,473	17,647	19,718	21,328	23,116	24,194	24,560
Dividend	6,340	6,879	8,049	8,976	9,851	11,137	12,141	14,261	16,414	18,210	19,528
DPS	7.35	8.11	9.49	10.58	11.61	13.13	14.31	16.81	19.35	21.46	23.02
Payout ratio	54.4%	52.0%	54.0%	56.0%	56.0%	56.0%	55.0%	60.0%	64.0%	68.0%	72.0%
Basic EPS	**11.25**	**13.23**	**15.21**	**16.48**	**18.24**	**20.80**	**23.24**	**25.14**	**27.24**	**28.51**	**28.95**
Diluted EPS	**11.16**	**13.14**	**15.10**	**16.36**	**18.11**	**20.65**	**23.08**	**24.96**	**27.05**	**28.31**	**28.74**
Core EPS	**13.62**	**15.48**	**17.44**	**18.76**	**20.59**	**23.27**	**25.83**	**27.82**	**30.01**	**31.34**	**31.74**

Source: Company Data and Citi Research

Figure 46. Roche Annual Cashflow Statement

SFr mlns	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Net Income	9,539	11,229	12,906	13,980	15,473	17,647	19,718	21,328	23,116	24,194	24,560
financial income (expense), net (Reported)	1,802	1,678	1,113	725	330	323	299	268	237	208	181
Income taxes	2,550	3,074	3,523	3,811	4,212	4,793	5,347	5,779	6,257	6,548	6,649
Income applicable to minority interests	234	334	347	359	371	384	397	410	424	438	453
Share of result of assoc. companies	-	-	-	-	-	-	-	-	-	-	-
Other	-	-	-	-	-	-	-	-	-	-	-
Operating profit	**14,125**	**16,314**	**17,889**	**18,875**	**20,386**	**23,148**	**25,761**	**27,786**	**30,034**	**31,388**	**31,843**
Depreciation of property, plant and equipment	1,891	1,982	2,071	2,159	2,244	2,328	2,411	2,491	2,571	2,648	2,724
Amortisation of Goodwill	-	-	-	-	-	-	-	-	-	-	-
Amortisation of Other Intangibles	530	538	547	555	563	572	580	588	597	605	613
Stock option charge	363	394	423	440	464	496	513	523	533	549	507
Impairment of Long-Term Assets	1,174	-	-	-	-	-	-	-	-	-	-
Charge for vitamin case	-	-	-	-	-	-	-	-	-	-	-
Charge for Pharma Division restructuring	-	-	-	-	-	-	-	-	-	-	-
Charge for major legal cases	-	-	-	-	-	-	-	-	-	-	-
Expense for defined benefit post-employment plans	280	(62)	(62)	(62)	(62)	(62)	(62)	(62)	(62)	(62)	(62)
Other adjustments	1,621										
Cash generated from operations	**19,984**	**19,166**	**20,868**	**21,966**	**23,595**	**26,482**	**29,202**	**31,326**	**33,672**	**35,128**	**35,625**
Decrease in Inventories	(523)	60	(130)	(114)	(83)	(248)	(266)	(156)	(189)	(245)	(124)
Decrease in Trade Receivables		(353)	(650)	(409)	(572)	(934)	(917)	(702)	(758)	(528)	(27)
Decrease in Other Receivables		(36)	(66)	(42)	(58)	(95)	(93)	(71)	(77)	(54)	(3)
Increase in Payables		73	134	84	118	192	188	144	156	109	6
Pharma Division restructuring costs paid	-	-	-	-	-	-	-	-	-	-	-
Legal Costs Paid	-	-	-	-	-	-	-	-	-	-	-
Payments made for defined benefit post-employment plans	(439)	-	-	-	-	-	-	-	-	-	-
Other operating cash flows	(688)	-	-	-	-	-	-	-	-	-	-
Income taxes paid	(3,329)	(3,074)	(3,523)	(3,811)	(4,212)	(4,793)	(5,347)	(5,779)	(6,257)	(6,548)	(6,649)
Total cash flows from operating activities	**15,005**	**15,836**	**16,632**	**17,675**	**18,788**	**20,604**	**22,768**	**24,762**	**26,547**	**27,862**	**28,828**
Purchase of property, plant and equipment (Capex)	(2,171)	(2,130)	(2,130)	(2,130)	(2,130)	(2,130)	(2,130)	(2,130)	(2,130)	(2,130)	(2,130)
Investment in intangibles	(235)	(251)	(251)	(251)	(251)	(251)	(251)	(251)	(251)	(251)	(251)
Disposal of property, plant and equipment, and intangible assets	107										
Acquisition of subsidiaries, associated companies, and products	(36)										
Divestments of subsidiaries, associated companies, and products	8										
Interest received	37	476	484	488	482	488	513	543	575	604	631
Dividends Received	2	3	3	3	3	3	3	3	3	3	3
Proceeds from Labcorp											
Sales/(purchases) of marketable securities, net and other investing cash flows	(2,226)	-	-	-	-	-	-	-	-	-	-
Total cash flows from investing activities	**(4,514)**	**(1,902)**	**(1,894)**	**(1,890)**	**(1,897)**	**(1,890)**	**(1,866)**	**(1,835)**	**(1,803)**	**(1,774)**	**(1,747)**
Proceeds from issue of long-term debt	2,698	-	-	-	-	-	-	-	-	-	-
Repayment of long-term debt	(4,326)	(2,642)	(7,337)	(6,824)	(30)	(30)	(30)	(30)	(30)	(30)	(30)
Transaction in own equity instruments (Purchase of Treasury)	(302)	-	-	-	-	-	-	-	-	-	-
Increase (decrease) in short-term borrowings	(534)	-	-	-	-	-	-	-	-	-	-
Interest paid	(1,514)	(2,154)	(1,598)	(1,213)	(812)	(812)	(812)	(812)	(812)	(812)	(812)
Dividends paid	(5,888)	(6,340)	(6,879)	(8,049)	(8,976)	(9,851)	(11,137)	(12,141)	(14,261)	(16,414)	(18,210)
Genentech / Chugai stock repurchases	-	-	-	-	-	-	-	-	-	-	-
Other financing cash flows	172	-	-	-	-	-	-	-	-	-	-
Total cash flows from financing activities	**(9,694)**	**(11,136)**	**(15,814)**	**(16,085)**	**(9,818)**	**(10,693)**	**(11,979)**	**(12,983)**	**(15,103)**	**(17,256)**	**(19,051)**
Net effect of currency translation on cash	(121)	-	-	-	-	-	-	-	-	-	-
Increase / (decrease) in cash	**676**	**2,798**	**(1,076)**	**(301)**	**7,073**	**8,021**	**8,923**	**9,944**	**9,640**	**8,831**	**8,029**
Cash at beginning of year	3,854	4,530	7,328	6,252	5,951	13,024	21,045	29,968	39,912	49,552	58,383
Cash at end of year	4,530	7,328	6,252	5,951	13,024	21,045	29,968	39,912	49,552	58,383	66,412
Free Cash Flow from Operations	23,449	12,771	13,656	14,763	15,936	17,721	19,873	21,864	23,645	24,950	25,964

Source: Citi Research

Figure 47. Roche Annual Balance Sheet

SFr mlns	2012A	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Long-term assets											
Property, plant and equipment	15,402	15,550	15,609	15,580	15,465	15,267	14,986	14,625	14,184	13,666	13,072
Goodwill	7,480	7,480	7,480	7,480	7,480	7,480	7,480	7,480	7,480	7,480	7,480
Other Intangible assets	4,214	3,927	3,631	3,327	3,015	2,694	2,365	2,028	1,683	1,329	967
Investments in associated companies	24	21	19	16	13	10	8	5	2	(0)	(3)
Financial Long-Term Assets	339	339	339	339	339	339	339	339	339	339	339
Deferred income tax assets	4,856	4,856	4,856	4,856	4,856	4,856	4,856	4,856	4,856	4,856	4,856
Post employment benefit assets	668	668	668	668	668	668	668	668	668	668	668
Other long-term assets	451	451	451	451	451	451	451	451	451	451	451
Total fixed assets	**33,434**	**33,292**	**33,052**	**32,717**	**32,287**	**31,766**	**31,153**	**30,452**	**29,663**	**28,788**	**27,830**
Current Assets											
Inventories	5,542	5,482	5,613	5,726	5,809	6,057	6,323	6,479	6,668	6,914	7,037
Trade Receivables	9,465	9,818	10,468	10,877	11,450	12,384	13,301	14,003	14,761	15,289	15,316
Other Receivables	963	999	1,065	1,107	1,165	1,260	1,353	1,425	1,502	1,556	1,558
Other current assets	1,071	1,071	1,071	1,071	1,071	1,071	1,071	1,071	1,071	1,071	1,071
Current income tax assets	339	339	339	339	339	339	339	339	339	339	339
Receivable from Bayer collected 010105	-	-	-	-	-	-	-	-	-	-	-
Marketable securities	9,461	9,461	9,461	9,461	9,461	9,461	9,461	9,461	9,461	9,461	9,461
Cash and cash equivalents	4,530	7,328	6,252	5,951	13,024	21,045	29,968	39,912	49,552	58,383	66,412
Total Current Assets	**31,371**	**34,498**	**34,269**	**34,532**	**42,319**	**51,617**	**61,816**	**72,690**	**83,354**	**93,012**	**101,195**
Total Assets	**64,805**	**67,790**	**67,321**	**67,249**	**74,606**	**83,382**	**92,969**	**103,142**	**113,017**	**121,801**	**129,025**
Non-Current Liabilities											
Long-term debt	17,860	15,218	7,881	1,057	1,027	997	967	937	907	877	847
Deferred income tax liabilities	1,394	1,394	1,394	1,394	1,394	1,394	1,394	1,394	1,394	1,394	1,394
Liabilities for post-employment benefits	7,253	7,191	7,129	7,067	7,005	6,943	6,881	6,819	6,757	6,695	6,633
Restructuring Provisions	176	176	176	176	176	176	176	176	176	176	176
Other Provisions	866	866	866	866	866	866	866	866	866	866	866
Provisions	1,042	1,042	1,042	1,042	1,042	1,042	1,042	1,042	1,042	1,042	1,042
Other non-current liabilities	319	319	319	319	319	319	319	319	319	319	319
Total Long-term liabilitites	**27,868**	**25,164**	**17,765**	**10,879**	**10,787**	**10,695**	**10,603**	**10,511**	**10,419**	**10,327**	**10,235**
Current Liabilities											
Short-term debt	6,730	6,730	6,730	6,730	6,730	6,730	6,730	6,730	6,730	6,730	6,730
Current income tax liabilities	2,210	2,210	2,210	2,210	2,210	2,210	2,210	2,210	2,210	2,210	2,210
Restructuring Provisions	522	522	522	522	522	522	522	522	522	522	522
Other Provisions	1,636	1,636	1,636	1,636	1,636	1,636	1,636	1,636	1,636	1,636	1,636
Provisions (current portion)	2,158	2,158	2,158	2,158	2,158	2,158	2,158	2,158	2,158	2,158	2,158
Accounts payable - trade and other	1,945	2,018	2,151	2,235	2,353	2,545	2,733	2,878	3,033	3,142	3,147
Accrued and other current liabilities	7,166	7,706	8,875	9,802	10,678	11,963	12,967	15,088	17,240	19,036	20,354
Total Current Liabilities	**20,209**	**20,821**	**22,124**	**23,135**	**24,128**	**25,606**	**26,799**	**29,063**	**31,371**	**33,275**	**34,599**
Equity											
Share capital	160	160	160	160	160	160	160	160	160	160	160
Own equity instruments	-	-	-	-	-	-	-	-	-	-	-
Retained Earnings and reserves	20,020	24,369	29,226	34,230	39,852	46,362	53,938	61,005	67,707	73,691	78,724
Fair value and other reserves	(5,686)	(5,292)	(4,869)	(4,429)	(3,965)	(3,469)	(2,956)	(2,433)	(1,900)	(1,351)	(844)
Total Shareholders' Equity	**14,494**	**19,237**	**24,517**	**29,961**	**36,046**	**43,053**	**51,142**	**58,732**	**65,967**	**72,500**	**78,040**
Minority interests	2,234	2,568	2,915	3,274	3,645	4,029	4,426	4,836	5,260	5,698	6,151
Liabilities + Shareholders' Equity	64,805	67,790	67,321	67,249	74,606	83,382	92,969	103,142	113,017	121,801	129,025
Net Debt (excl pension)	10,599	5,159	(1,102)	(7,625)	(14,728)	(22,779)	(31,732)	(41,706)	(51,376)	(60,238)	(68,296)
Net Debt (inc pension)	17,852	12,350	6,027	(558)	(7,723)	(15,836)	(24,851)	(34,887)	(44,619)	(53,543)	(61,663)

Source: Company Data and Citi Research

Appendix A-1

Analyst Certification

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

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