

Immunotherapy: Bigger, Broader, Bladder

Writing the Next Chapter for the Cancer Revolution



- **What's New- Immunotherapy for (almost) all:** we provide a cutting edge update to our May 2013 report ([Immunotherapy – The Beginning of the End for Cancer. - Transforming Cancer into Chronic Disease](#)). This report is technical in nature but we provide a PM summary (pg 10-12). We are confident that peak revenues will reach and potentially exceed our previous \$35bn estimate. We reiterate our BUY recommendations on key immunotherapy winners: BMY Roche and Ono. Legacy cancer companies (SAN, LLY, NVS) continue to have little exposure.
- **Consensus still only reflects c.30% of potential. Next stop bladder cancer.** Immunotherapy will become the cornerstone for the majority of solid and blood cancers. We anticipate compelling data for Roche's anti-PDL1 in bladder cancer (\$4bn pa potential) at ASCO 2014 (June), with multiple additional cancers to follow including, breast, prostate and blood cancers.
- **Updating immunotherapy basket.** We update our immunotherapy basket (up 35% since inception) and also identify a number of companies that are exposed to the immunotherapy space.
- **We have added BUY rated Roche to Citi's European Focus List and we reiterate our BUY rating.** Our PT increases from SFr 280 to SFr300 (>20% ETR). We anticipate compelling efficacy data with Roche's anti-PDL1 in bladder cancer at ASCO 2014, a novel indication with \$4bn pa revenue potential. The market is overlooking the growing breadth of Roche's clinical IT portfolio that encompasses vaccines, multiple checkpoints among others. [Roche Holding AG \(ROG.VX\) - Immunotherapy Ninja](#). BUY SFr300 TP. Adding to Citi Focus List
- **"Personalized immunotherapy" is the future.** Diagnostic advances will enable "personalized cancer immunotherapy", analogous to the current drug based management of HIV. Diagnostics can predict: (i) disease prognosis, (ii) baseline responsiveness to immunotherapy (iii) adverse event risk. We highlight emergent PCR based diagnostic companies Adaptive Biotechnologies (QuanTILfy assay) and ImmunID (ImmunTraCkeR assay)
- **Long term revenue risk to BUY-rated Celgene and Gilead among others.** The use of short duration anti-PD1/L1 drugs in several blood cancers (including CML, MM, and CLL) as well as HIV could allow many patients to ultimately cease their current chronic, expensive, oral therapies and attain a "treatment free remission" minimizing treatment payor costs.
- **Chemokine inhibitors, a new blockbuster class.** We expect data from oral CCR5 inhibitor Selzentry (PFE) in colorectal cancer in 1Q14. We anticipate multiple chemokine combinations with PD1 targeting agents. Pfizer, Merck, Incyte, BMY and even Sanofi all have interesting chemokine compounds.
- **Cancer vaccines are an undervalued and invaluable induction strategy** to address non-inflamed/immunogenic cancers that are otherwise non responsive to checkpoint inhibitors such as PD1. We anticipate the gene signature data for GSK's MAGE-A3 in 1Q 2015 for both melanoma and lung cancer. We discuss outcomes.

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See Appendix A-1 for Analyst Certification, Important Disclosures and non-US research analyst disclosures.

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Figure 1. We prefer Roche, Novartis and Novo Nordisk in EU Large-Cap Pharma, Roche and Novartis are on the Citi EU Focus List. BMY remains our preferred pick in US Pharma.

		Rating	Price Target	Investment Thesis	Cancer Immunotherapy	“Shrink, Smarten, Spin”	Biologics	Vaccines	Diagnostics	Consumer Health	Emerging Markets	Generics	Animal Health
<div>Most Favoured</div> <div>↑</div> <div>↓</div> <div>Least Favoured</div>	Roche	Buy	CHF 300.00	Innovation, immunotherapy	✓✓✓	✓✓	✓✓✓		✓✓✓		✓✓		
	Bristol Myers-Squibb	Buy	\$60.00	Immunotherapy	✓✓✓	✓✓✓	✓✓✓				✓		
	Novartis	Buy	CHF 83.00	Innovation vs LOE. Restructuring	✓	✓	✓	✓	✓	✓	✓	✓✓✓	✓
	Novo Nordisk	Buy	DKK 280.00	Emerging markets, diabetes		✓	✓✓✓				✓✓		
	Shire	Buy	£36.00	Rare diseases innovation		✓✓	✓✓				✓		
	Bayer	Buy	€110.00	Xarelto, Emerging Markets		✓	✓✓		✓	✓✓✓	✓✓	✓	✓
	Pfizer	Buy	\$31.00	Cost, WC De-equitisation	✓	✓✓✓	✓✓	✓✓			✓✓	✓	
	Eli Lilly	Buy	\$60.00	Pipeline, base incl. Alimta, EM		✓✓✓	✓✓✓				✓		✓✓
	AstraZeneca	Neutral	£35.00	Shrink research. De-equitisation growth drivers	✓✓✓	✓✓	✓	✓				✓	
	GlaxoSmithKline	Neutral	£18.10	Pharma 2.0 diversification	✓	✓✓✓	✓	✓✓✓		✓✓✓	✓✓		
	Sanofi	Neutral	€73.00	Return to sustainable growth		✓✓✓	✓	✓✓✓		✓✓✓	✓✓✓	✓	✓✓✓
	Merck KGaA	Neutral	€122.00	Cost cutting, business development	✓	✓	✓✓	✓	✓	✓	✓		
Merck & Co	Neutral	\$44.00	Cost, WC reduction pipeline	✓		✓✓	✓✓✓		✓	✓		✓✓✓	

Source: Citi Research

Figure 2. Large-Cap Pharma Valuation

Company	RIC	Analysts		Current Price	Market Cap (\$bn)	Rating/ Risk	Price	Target % Upside	ETR	2014E Multiple PE EV/EBITDA	2014-19E CAGR Sales	EPS	2014E Div Yield	
European Large Cap Pharma														
AstraZeneca	AZN.L	Andrew S Baum	GBP	38.8	80.3	Neutral	35.0	-10%	-5%	14.0	9.7	2.1%	6.7%	4.4%
Bayer	BAYGN.DE	Andrew S Baum	EUR	95.9	108.1	Buy	110.0	15%	16%	14.6	10.1	5.3%	10.4%	2.5%
GlaxoSmithKline	GSK.L	Andrew S Baum	GBP	1,603.0	127.8	Neutral	18.1	-99%	-94%	14.5	12.4	3.3%	7.9%	5.2%
Novartis	NOVN.VX	Andrew S Baum	CHF	72.4	218.2	Buy	83.0	15%	18%	14.4	13.1	3.3%	11.1%	3.2%
Novo-Nordisk	NOVOB.CO	Peter Verdult	Dkr	233.8	118.1	Buy	280.0	20%	21%	22.9	17.2	9.7%	15.9%	2.1%
Roche	ROG.VX	Andrew S Baum	CHF	253.7	243.4	Buy	300.0	10%	13%	15.6	11.4	6.0%	11.0%	3.4%
Sanofi	SASY.PA	Peter Verdult	EUR	71.7	129.5	Neutral	73.0	2%	5%	13.9	9.6	3.9%	8.3%	3.9%
EU Large-cap Pharma (mkt-cap wt avg)										15.6	12.1	4.9%	10.5%	3.5%
US Large Cap Pharma														
AbbVie	ABBV.N	Not Rated	USD	48.9	77.8	Not Rated	NR	NR	NR	15.7	11.2	NA	NA	3.4%
Bristol Myers	BMJ.N	Andrew S Baum	USD	50.3	82.9	Buy	60.0	9%	12%	27.1	20.5	8.1%	20.4%	2.9%
Eli Lilly	LLY.N	Andrew S Baum	USD	53.2	59.9	Buy	60.0	13%	16%	19.3	9.6	4.5%	15.5%	3.7%
Johnson & Johnson	JNJ.N	Matthew J Dodds	USD	90.0	254.0	Buy	111.0	23%	26%	15.5	9.7	NA	NA	2.9%
Merck	MRK.N	Andrew S Baum	USD	54.8	160.0	Neutral	44.0	-20%	-17%	16.2	11.0	0.8%	4.9%	3.2%
Pfizer	PFE.N	Andrew S Baum	USD	31.2	202.3	Buy	31.0	-1%	2%	13.8	7.8	1.8%	7.4%	3.4%
US Large-cap Pharma (mkt-cap wt avg)										16.7	10.7	2.8%	9.5%	3.2%
Global Large-cap Pharma (mkt-cap wt avg)										16.1	11.4	3.9%	10.1%	3.4%

Source: Citi Research. 10th February

Writing the Next Chapter for the Cancer Revolution

Despite the valuation uplift for immunotherapy sponsors over the last 8 months, we continue to see extraordinary opportunity for value creation as the market for cancer immuno-therapeutics is set to increase by at least 3 fold over the next 5 years. In this update to our May 2013 in-depth report [*Immunotherapy – The Beginning of the End for Cancer. - Transforming Cancer into Chronic Disease*](#), we discuss anticipated next developments relating to: (i) market expansion to new indications, notably bladder cancer in near term; (ii) multi-modality fragmentation of immunotherapy; (iii) next-generation immunodiagnostics. We also update our immunotherapy basket and identify relative winners/losers. **At current valuation levels, we see the greatest relative upside for BUY-rated Roche. We continue to view BUY rated BMY in the US and Roche in EU as the key potential beneficiaries in this critical segment.**

Perceived market opportunities for immunotherapy set to expand. Bladder cancer at ASCO, with other blood and solid tumour data close behind.

PCR based immunoassays will revolutionize outcomes. We see many parallels with the evolution of HIV care.

Therapeutic cancer vaccine combinations and chemokine blockers will prove critical in addressing a third of cancer patients with poorly immunogenic tumours.

We anticipate Roche to present compelling data in advanced bladder cancer at ASCO 2014 (June). We estimate \$4bn pa potential opportunity.

Key developments to watch for over the next 12 months:

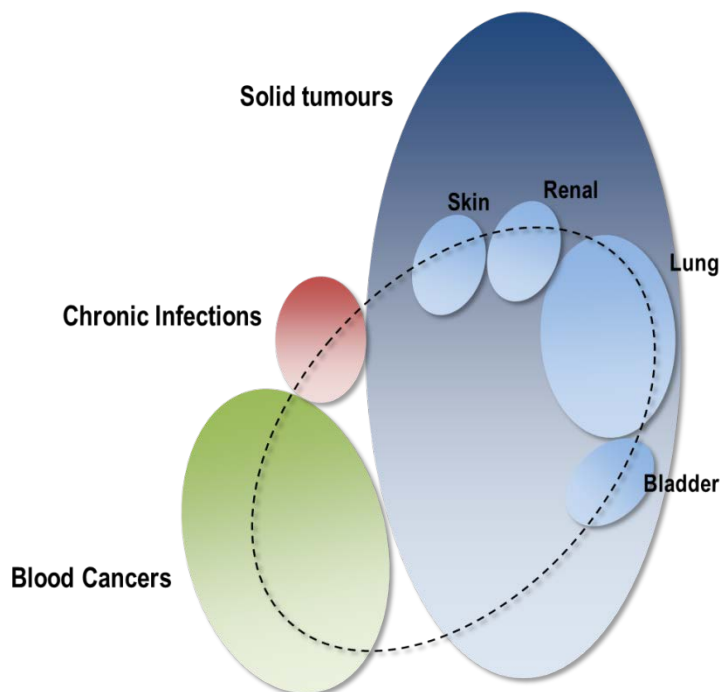
- 1. Significant market expansion, starting with bladder cancer.** We anticipate data at ASCO 2014 for Roche's anti-PDL1 in bladder cancer, a \$4bn per annum opportunity. Beyond bladder, we see material opportunities in myeloma, gastric, head and neck, cervical and liver cancer among other indications. (pg 17)
- 2. Novel diagnostic tests.** The evolution, adoption and implementation of prognostic and predictive TIL-based¹ diagnostic tests will translate into personalized immunotherapy with likely radically improved patient outcomes. We see parallels with evolution of HIV treatments. (pg 21)
- 3. The market fragmentation of immunotherapy treatment modalities** to include therapeutic cancer vaccines, chemokine inhibitors, bispecific TCRs among several other treatment modalities. We anticipate increasing clinical validation of chemokine and therapeutic cancer vaccines over the next 12 months (pg 26)
- 4. The ability to address the poorly immune-responsive cancer.** The integration of diagnostics and novel therapeutics to induce immune-responsiveness in a tumour that is poorly immunogenic at baseline; if successful, this would provide upside to our \$35bn peak estimates. We discuss the continuum of immunogenicity across cancers and emergent technologies to optimize treatment outcome, highlighting potential winners. (pg 23)

We anticipate Roche to present compelling data in advanced bladder cancer with their anti-PDL1 at ASCO 2014 (June). Strong data in this tough-to-treat cancer would be an important near term catalyst to persuade the market to start valuing opportunity for immunotherapy beyond the initial lung, skin and renal cancer indications, we believe. While estimates for immunotherapy related assets have significantly increased since our May 2013 report ([*Immunotherapy – The Beginning of the End for Cancer. - Transforming Cancer into Chronic Disease*](#)), neither estimates nor valuations recognize the potential for immunotherapy use beyond the three initial indications. Not only is advanced bladder cancer a sizeable revenue opportunity (\$4bn per annum), but it also underscores the potential of immunotherapy to expand across multiple additional indications.

¹ TILs or Tumour infiltrating lymphocytes are white blood cells that have left the bloodstream and migrated into a tumour.

PD1 targeted agents are set to become the cornerstones for c.60% of advanced solid tumours, hematologic tumours and even infectious diseases.

Figure 3. We anticipate Immunotherapy to be the cornerstone of care in >60% of Advanced Solid and Haematologic Cancers. PD1 mediated therapies are likely to be the backbone of immunotherapy with additional utility in chronic infections (HIV, HBV, Malaria, TB etc).



The dotted line represents the opportunity set of tumours that are immuno-responsive.

Source: Citi Research, American Cancer Society

Roche and BMY remain our preferred names to play Immunotherapy theme. We however, continue to recommend a basket/portfolio approach

BUY-rated Roche and BMY remain our key investment ideas. We continue to see BUY-rated Roche and BMY as the likely dominant forces in immuno-oncology for the next 5-10 years. Our BUY rating on both names reflects our belief that the current valuation only partly reflects the value of their immuno-oncology pipeline (Figure 3). Our forecasts for both names are up to 20% ahead of consensus post 2017. We have reiterated our BUY rating on BMY and increased our price target to \$55 from \$60 previously.

Reiterating BUY on Roche. PT SFr 300. Adding to Citi Focus List. We highlight: (i) Roche's underappreciated broad IT portfolio, (ii) \$4bn pa commercial opportunity in bladder cancer, (iii) potential for Avastin/PD-L1 to be the first combination treatment to be approved.

Reiterating BUY on Roche. PT SFr 300. Adding to Citi Focus List. Following AZN's re-rating in the past three months ([Looking For A Deal, Waiting For The Pipeline. NEUTRAL](#) dated 21/Nov/2013), Roche's immunotherapy portfolio looks the most undervalued in relation to its DCF derived NPV compared to peers. We re-iterate our BUY thesis on Roche, increasing our target price from SFr 280 to SFr 300, and added Roche to The Citi Focus List. Today's companion Roche report highlights: (i) the breadth of Roche's immunotherapy clinical pipeline; (ii) the \$4bn pa commercial potential of the novel advanced bladder cancer opportunity; (iii) the potential for Roche's anti-PDL1 + Avastin combination to be the first approved immunotherapy combination following the recent delayed development of BMY's dual checkpoint inhibitor regimen (Yervoy+nivolumab)

Figure 4. Our ests on our key immunotherapy participants are up to 20-25% ahead of cons

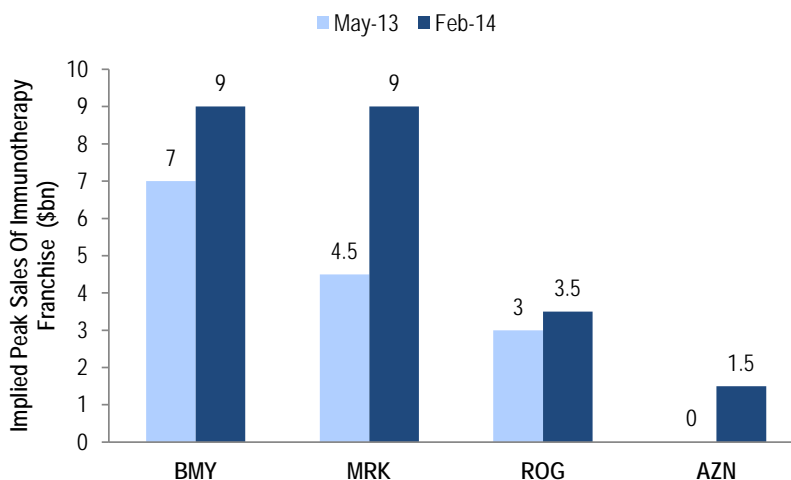
EPS estimates		2014	2015	2016	2017	2018
ROG	Citi	15.3	17.3	18.9	21.3	24.0
	Cons	15.4	16.6	17.6	18.9	20.0
	Delta	-1%	4%	8%	12%	20%
BMY	Citi	1.7	1.9	1.7	2.2	2.9
	Cons	1.7	1.8	1.7	1.9	2.4
	Delta	0%	4%	3%	14%	20%
AZN	Citi	4.6	4.5	4.7	4.4	5.5
	Cons	4.6	4.5	4.5	4.2	4.4
	Delta	0%	0%	6%	6%	25%

Source: Citi Research, Consensus from Factset

AZN's overlooked oncology pipeline analyzed in depth in recent report. Upside from IT for MRK offset by pressures in base business, mainly diabetes. Both AZN and MRK feature in our IT basket.

We published an extensive analysis of AZN overlooked oncology pipeline in our November 2013 report ([Looking For A Deal, Waiting For The Pipeline. NEUTRAL](#)). Our EPS forecasts are c.25% ahead of consensus post 2017. Separately, while we applaud Merck's thoughtful development of MK-3475 (their anti-PD1) and extensive recent partnering in immuno-oncology, we remain concerned over the vulnerability of existing/future cash flows to competitive pressures in the diabetes, HIV, and pneumonia space. We also feel more confident in the extensive oncology development experience and materially broader organic immunotherapy pipelines of BMY and Roche. Both AZN and MRK are included in our immunotherapy basket, however.

Figure 5. A rough estimate of the implied peak sales potential of the immunotherapy franchises of the major players in the space: Roche IT portfolio potential still largely under-appreciated.



Source: Citi Research, Company reports

Updating immunotherapy basket. Our immuno-oncology basket has increased 35% in valuation since inception, outperforming broader markets by 25% (Figure 6). We update the immunotherapy basket (Figure 8) and also identify a number of companies that are exposed to the immunotherapy space (Figure 7).

Figure 6. 25% Outperformance of IO Basket since May 2013



Source: Citi Research, DataStream. Note: We have excluded Vical post Allovectin melanoma failure. See Figure 38 for past performance data.

Figure 7. Exposure to Immunotherapy

Private companies
Adaptimmune
Adaptive Biotech
Aduro
Beigene
Immatics
Immunocore
Jounce
Juno

Source: Company Reports

Figure 8. Citi's Immunotherapy Basket, CGRBIMMU

Amgen
AZN
Bristol Myers Squibb
GSK
Merck
Novartis
Roche

Source: Citi Research

Figure 9. Roche now has a very broad portfolio of immunotherapeutics under development, rivaling BMY.

	BMJ	ROG	AZN	MRK	GSK	PFE	NOVN	LLY	MRCG	AMGN	CELG
Checkpoint blockers											
CTLA4	✓		✓			✓					
PD1	✓		✓	✓	★						
PD-L1	✓	✓	✓						✓		
LAG-3	✓										
KIR	✓										
CSF1R		✓									
Checkpoint costimulators											
CD137	✓					✓					
CD40		✓				✓					
OX40			✓								
TGFβ								✓			
Chemokine Blockers											
	✓	✓		✓		✓					
Cell therapy											
							✓				✓
Therapeutic Vaccines											
		✓			✓				✓		

Source: Citi Research, Company reports. Star indicates uncertain stage of development. Note: this includes only disclosed assets that have entered clinical development. There are multiple assets in pre-clinical development that are not included in this list.

Chronic therapies for blood cancers and HIV are likely the new category of potential losers from the emergence of immunotherapy. We see potential risk for the likes of Tassigna (NOVN), Sprycel (BMJ), Revlimid (CELG) among others.

Durable treatment free remissions seen with IT is attractive from both patient and payor perspective.

New potential long term losers: Celgene, Gilead among others. In our May 2013 report, we highlighted Roche's Avastin and Lilly's Alimta as two potential current branded losers in the face of emergent competition from immunotherapeutic agents. We now see additional potential future downside risk to estimates 2019+ for agents used in the maintenance setting for blood based cancers. Pre-clinical data suggests that short term PD1-small molecule combinations could trigger treatment free remission (TFR), allowing the patient to cease chronic therapy with the small molecule/antibody while preserving disease control.

This new paradigm, if effective, has multiple attractions for the patient and the payor in terms of an absence of adverse events and given a material reduction in per-patient treatment costs. Discontinuation trials with Sprycel-IFN and Sprycel-PD1 are ongoing in CML. In addition, we anticipate similar trials in Multiple Myeloma with potential risk to current incumbents including BUY-rated Celgene, Buy-rated Amgen's Kyprolis and Neutral-rated Takeda's Velcade. We caveat that TFR will not be achieved in all patients regardless of the addition of anti-PD1 agents and treatment discontinuation will be contingent on evidence that patients can regain disease control post relapse.

Immunotherapy-the Portfolio Manager Recap

Despite the valuation uplift for immunotherapy sponsors over the last 8 months, we continue to see extraordinary opportunity for value creation as the market for cancer immuno-therapeutics is set to increase by at least 3 times over the next 5 years. In this update to our May 2013 in-depth report ([Immunotherapy – The Beginning of the End for Cancer. - Transforming Cancer into Chronic Disease](#)), we discuss anticipated next developments relating to: (i) market expansion to new indications, notably bladder cancer in near term; (ii) multi-modality fragmentation of immunotherapy; (iii) next-generation immunodiagnostics. We also update our immunotherapy basket and identify relative winners/losers. At current valuation levels, we see the greatest relative upside for BUY-rated Roche. We continue to view BMJ in the US and Roche in EU as the key potential beneficiaries in this critical segment.

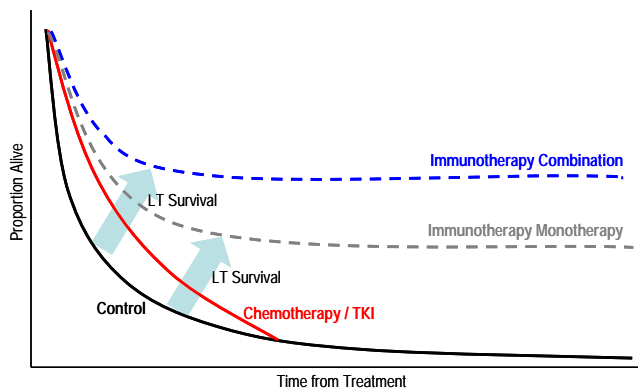
Cancer accounts for ¼ deaths in the West with an enormous social cost. Immunotherapy can potentially transform >60% into a chronic disease-like state

Durability of existing chemotherapy is very short. In contrast, immunotherapy can lead to very durable responses (lasting years). Strong parallels with evolution of HIV treatment.

Cancer and Cancer Immunotherapy: a recap. Cancer is the developed world's second most common cause of death accounting for a quarter of all deaths with an economic cost in 2008 estimated at \$200bn per annum. Immunotherapeutic approaches leverage the patient's immune system to eliminate or slow the growth and spread of cancerous cells with the potential to dramatically improve the economic and medical outlook for cancer patients. 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.

While existing chemotherapy or even newer oral drugs 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 or longer, due to the induction of an ongoing immunological memory, targeting cancer cells for an indeterminate length of time and making 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. Further background on immunotherapy can be found in our May 2013 report hyperlinked above.

Figure 10. Immunotherapy responders can experience a dramatic impact on survival compared with conventional chemotherapy due to durability of response.



Source: Citi Research

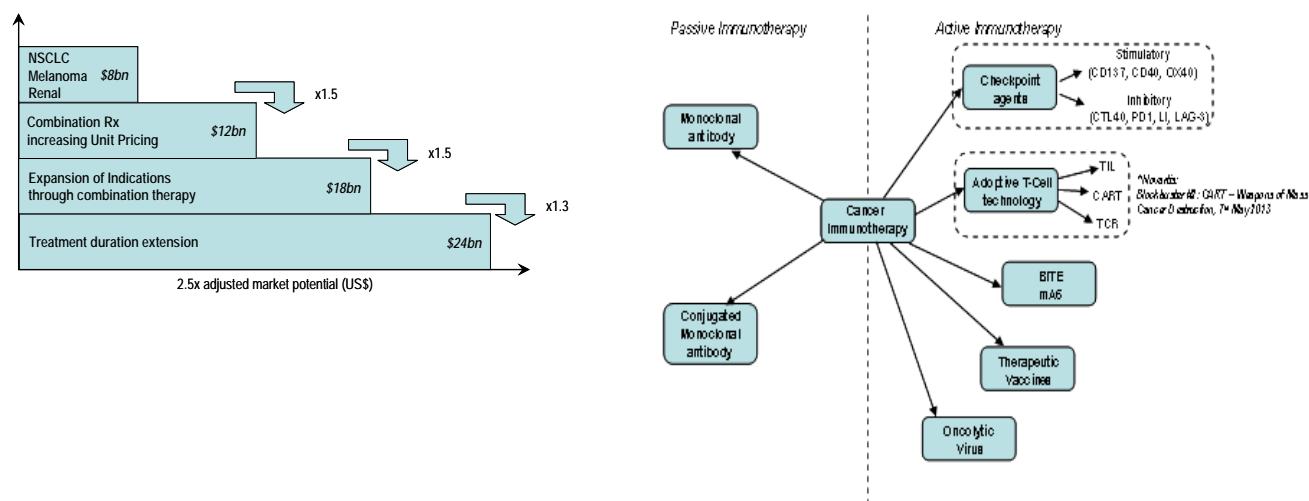
Despite re-rating, current estimates for immunotherapy are reflecting the initial three indications (<25% of total advanced cancers)

Our conviction in our \$35bn peak market potential for immunotherapy has further strengthened since our May 2013 report. While, valuations for immunotherapy asset holders have increased (as our immunotherapy basket's outperformance shows), equity markets are now discounting the contribution of immunotherapy in only the three initial solid tumour indications under development (Figure 12. Current estimates include only sales in metastatic melanoma, NSCLC and renal cell carcinoma. Potential size of the immunotherapy opportunity across multiple tumour types and chronic viral infections is 3x this size.) which represent less than a quarter of all the cancers in the developed world.

There is initial evidence that PD-1 mediated agents might have activity in chronic infectious diseases such as HIV, Hepatitis B, TB and Malaria acting via reversing T cell anergy and enabling the immune system to overcome or better control chronic infective disease. We continue to exclude adjuvant indications from our market forecasts given lack of confirmatory evidence.

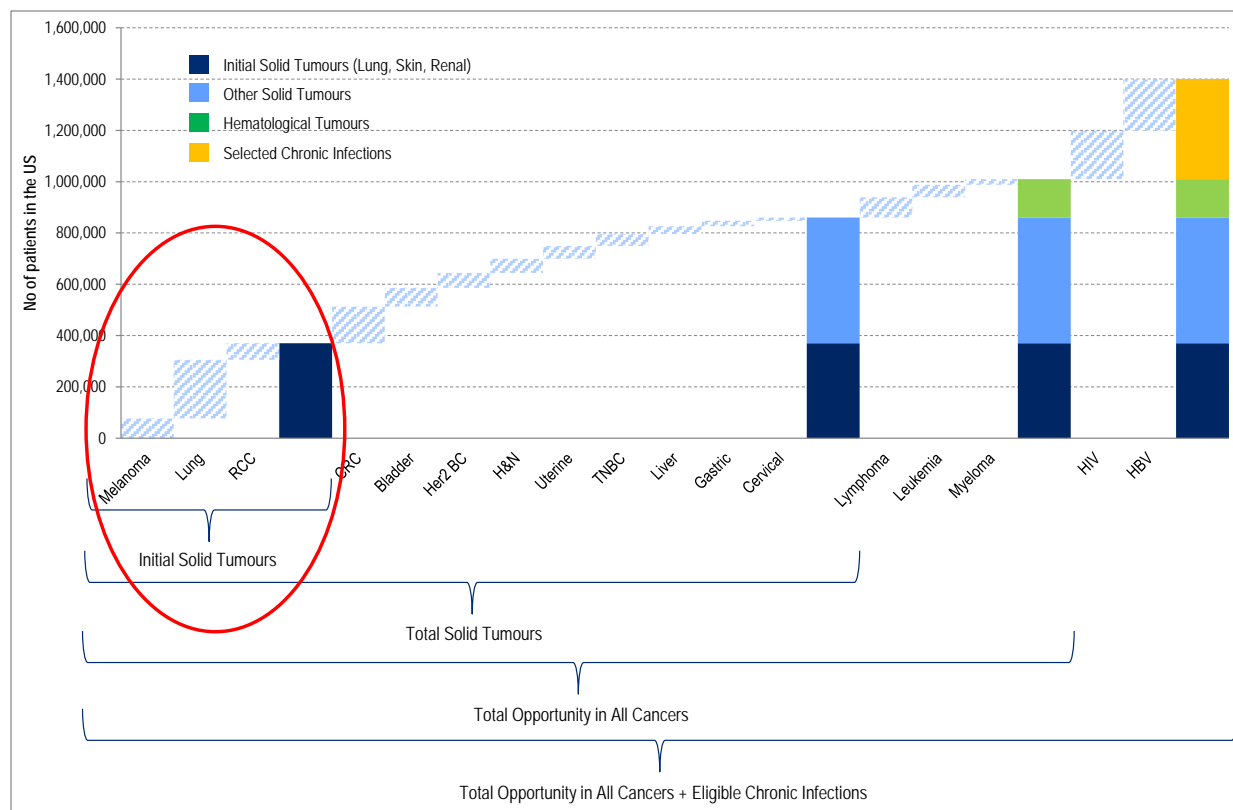
Our assessment of scale of the market potential for immunotherapy is summarized in (Figure 12. Current estimates include only sales in metastatic melanoma, NSCLC and renal cell carcinoma. Potential size of the immunotherapy opportunity across multiple tumour types and chronic viral infections is 3x this size.)

Figure 11. Market estimates for immunotherapy opportunity are materially under-represented.



Source: Citi Research

Figure 12. Current estimates include only sales in metastatic melanoma, NSCLC and renal cell carcinoma. Potential size of the immunotherapy opportunity across multiple tumour types and chronic viral infections is 3x this size.



Source: Citi Research, American Cancer Society.

Note: 1) we have excluded tumours that are less immunogenic in nature and where mechanistic rationale for utility of immunotherapy is less well-established.

2) we have included only 25% of chronic HIV and HBV patients as a rough estimate of the eligible patient population.

Immunotherapy for (Almost) All.

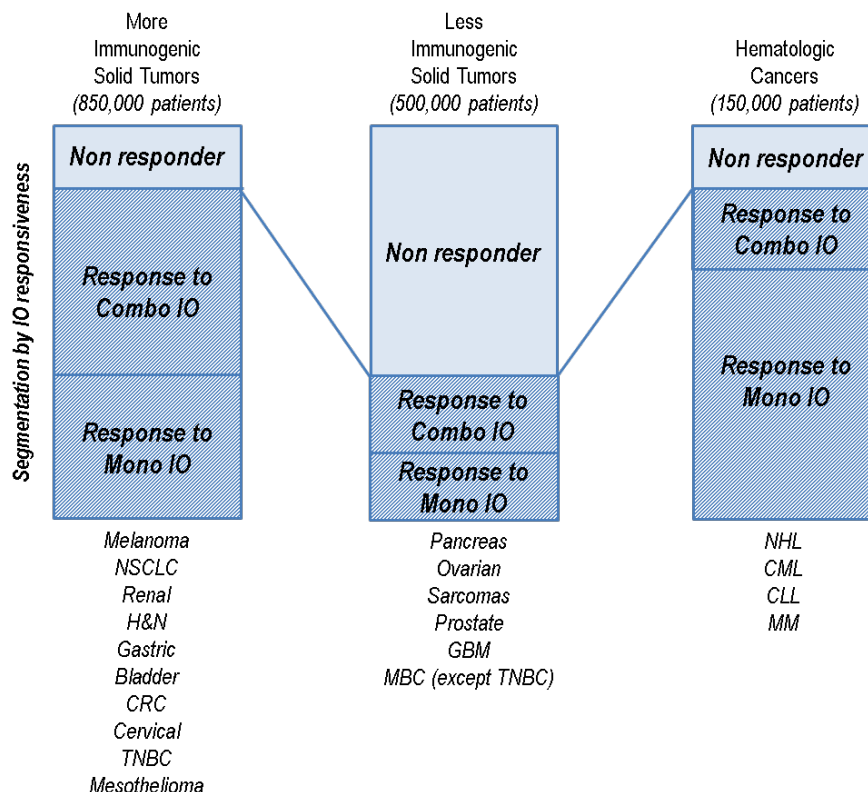
Immunotherapy is set to become the treatment goal for almost all advanced cancers.

Making a cancer immune-responsive is set to become the over-riding treatment goal for oncologists across almost all indications. Immunotherapy is the only treatment through which advanced cancer can potentially be transformed without the need for chronic administration of agents and their associated toxicities. The use of precision medicine (use of personalized therapeutics) will shift from the current dominant role of chronic targeted therapies, to a more subsidiary role in enhancing the activity of immunotherapeutic agents. The evolution of tissue and blood immunodiagnostics (discussed in pg. 21) will open up a new paradigm of pharmacologic cancer care for solid and hematologic tumours outlined in Figure 15

Immunodiagnostics will transform development and treatment strategies in oncology and dramatically transform outcomes for the many, rather than the few.

Immunotherapy will evolve into the dominant treatment modality for almost all advanced cancers by 2025, we believe. The primary treatment goal for almost all advanced cancers will be to maximize the responsiveness of a given patient's cancer to immunotherapy. Molecular diagnostics can already identify which patients are likely responsive at baseline to immunotherapies, a measure that can then be monitored and treatment modified as the disease progresses. Patients without an immune-responsive tumour micro-environment will be addressed through a wide array of approaches (we highlight cancer vaccines in particular) designed to elicit and maximize immune-responsiveness. The percentages of patients more, or less, likely to respond to immunotherapy at baseline (as determined by tumour T-cell infiltrates) will differ across indications and are schematically represented in Figure 13

Figure 13. Cancers can be segregated by their likely responsiveness to immunotherapy. Immunogenic and Hematologic Cancers account for two-thirds of the total prevalence of stage IV cancers. We believe that combination therapies (PD1+vaccines/other modalities) will also transform many non-immunogenic cancers by increasing responsiveness to immunotherapy.



Source: Citi Research, American Cancer Society

Immuno-responsiveness is determined by the interaction of the patient's immune system with the tumour. Immunogenic cancers include: (i) mutagen induced, (ii) virally mediated, (iii) hematologic

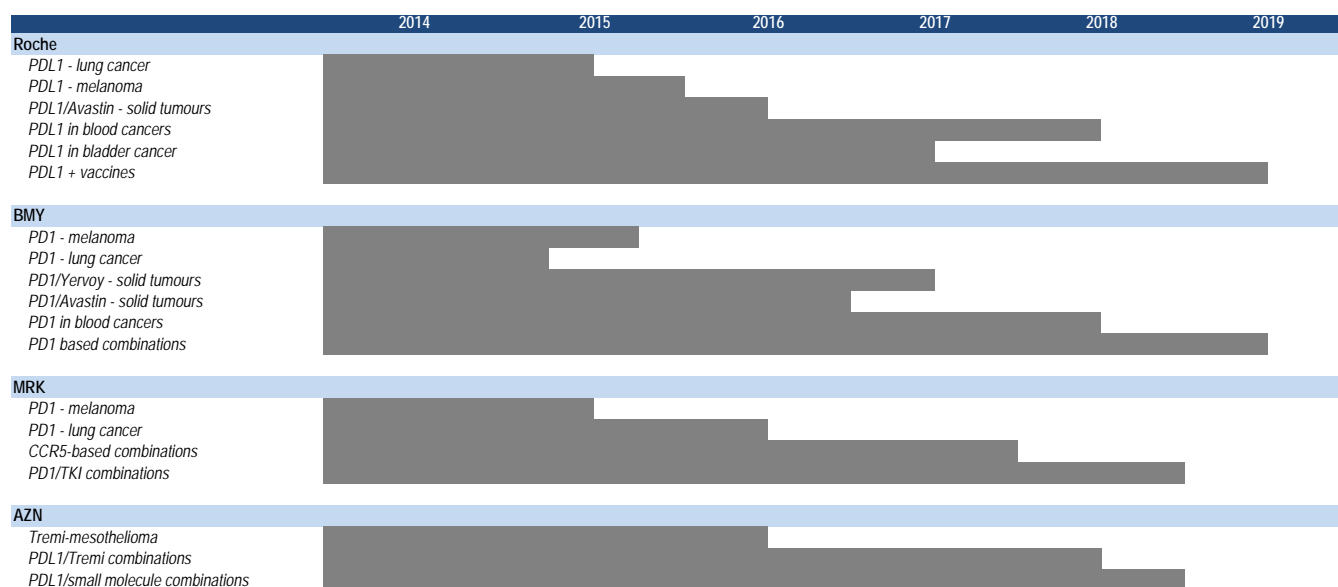
Potentially “Immuno-responsive” cancers account for 2/3rds of the total Western cancer incidence. We anticipate 20-40% responsiveness in this patient cohort with baseline PD1 mediated baseline monotherapy.

1. **Cancers that are induced through exposure to a known mutagen appear to be among the most responsive to immunotherapeutic approaches.** Confirmed examples to date include NSCLC (smoking induced), malignant melanoma (UV light induced) and mesothelioma (asbestos induced). In a similar manner, we anticipate bladder cancer to be highly immune-responsive given the strong correlation between incidence and smoking or industrial chemicals exposure.
2. **Virally mediated cancers are likely to generate strong responses to immunotherapy** given the detection of non-host protein by T cell receptors (TCRs). Likely responsive virally induced cancers include: (i) head and neck (HPV), (ii) Cervical (HPV), (iii) hepatocellular carcinoma (HCV) among others
3. **We anticipate strong responsiveness to mono or combination immunotherapy in hematologic cancers** given the high incidence of frequent somatic mutations and the likely minimal inhibitory impact of regulatory T-cells (T-regs). Potential disease targets include Multiple Myeloma, CML, DLBCL and CLL as described below.

The expansion of the market opportunity in cancer to beyond NSCLC, melanoma and renal cancer rests on

- (i) identification of patients with immunoresponsive cancers. *We discuss the evolution and application of immunodiagnostics on pg 21*
- (ii) ability to transform patients with non-immunoresponsive disease to an immunoresponsive phenotype through priming strategies. *We discuss approaches to enhance immune-responsiveness on pg 23*

Figure 14. Rough timeline of potential immunotherapy launches for the key players in the space: Roche Avastin/PDL1 combination could potentially be the first IT combination



Source: Citi Research, Company data.

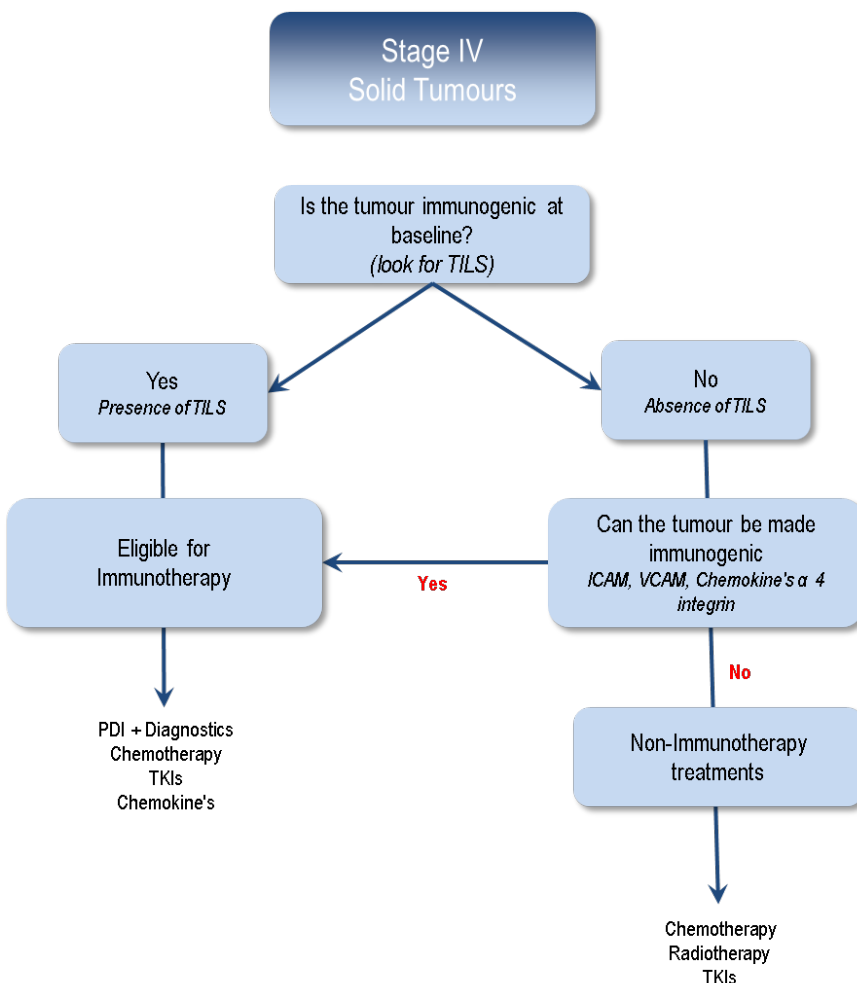
Cancer Rx 2025. Immunotherapy at the Core

A new paradigm for metastatic cancer care: characterize the tumour microenvironment pre-treatment and over the treatment course.

The new decision tree for advanced cancer care is outlined in Figure 15. The adoption of the new treatment paradigm is enabled by the implementation of powerful immunoassays coupled with the emergence of multiple priming strategies.

How does it work? The majority of newly diagnosed patients with advanced cancers with an inflammatory T cell infiltrate will be candidates for a PD1/L1 targeted agent. Patients without a T-cell infiltrate tumour at baseline are very unlikely to respond to anti-PD1/PDL1 based therapy given the absence of T cell trafficking to the site of the malignancy. We are optimistic that a significant percentage of these patients will become immune-responsive following additional treatment interventions designed to elicit an inflammatory CD8 T cell infiltrate in the tumour micro-environment. The minority of cancers that remain immune-resistant despite priming (likely to include pancreatic among others) will require other treatment strategies aside from immunotherapy.

Figure 15. Immunotherapy is the new over-riding goal for advanced cancer care. Diagnostically determined poorly immune-responsive cancers will be primed to optimize immunotherapy outcomes. PCR and IHC based diagnostics become critical for treatment management and patient selection.



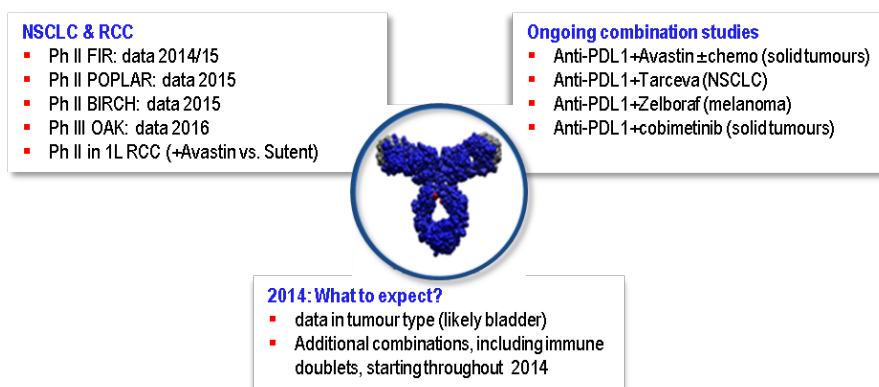
Source: Citi Research

Anti-PDL1 in Bladder Cancer: A Novel \$4 pa opportunity.

We suspect that Roche's anti-PDL1 has shown activity in bladder cancer, a \$4bn per annum opportunity. We anticipate data at ASCO 2014 (June)

Compelling data with anti-PDL1 among other solid and blood cancers expected at ASCO 2014. We anticipate that AZN will showcase data from its growing portfolio of immune-therapeutics at ASCO. We anticipate that the company will present compelling data with their anti-PDL1 across several indications, most notably in previously undisclosed bladder cancer from their ongoing 344 patient phase I trial. Bladder cancer is sizeable and poorly treated indication with little treatment advances over the last 15 years. We calculate a peak revenue potential of \$4bn for this indication alone.

Figure 16. Multiple data readouts for Roche anti-PDL1 over 2H2014/2015.



Source: Citi Research, Company data

We suspect anti-PDL1 has shown significant activity in bladder cancer

Bladder cancer like melanoma and NSCLC is mutagenic, associated with smoking and industrial chemicals

Our May 2013 report ([Immunotherapy – The Beginning of the End for Cancer. - Transforming Cancer into Chronic Disease](#)) highlights that cancers with mutagenic causation are most likely responsive to anti-PD1/ immunotherapy at baseline. These include lung cancer (smoking), mesothelioma (asbestos), and skin cancer (UV radiation). Like these aforementioned cancers, bladder cancer incidence is strongly associated with the important mutagens of smoking, chemicals and previous chemotherapy. Further evidence for the immune-responsiveness of bladder cancer is the strong benefit TCC (transitional cell carcinoma) derive from of intra-bladder administration of Bacillus Calmette-Guérin or BCG (a much older immunotherapy) which remains the standard of care.

Prior BCG treatment may potentiate immunotherapy

In addition to seeing if our thesis relating to bladder cancer as PDL1 responsive is confirmed, we are also intrigued to see what percentage of responders received prior BCG therapy. We suspect that patients who experienced prior treatment with BCG vaccine have more profound response rates compared with those patients who were BCG naive. Data for a more profound response in BCG-treated patients lends significant support for the utility of therapeutic vaccines to enhanced antigen presentation prior to checkpoint blockade therapy. As we have highlighted, Roche has recently added two very attractive cancer vaccine platforms (Inovio and Immatix) to its portfolio.

**Patient selection and prior BCG exposure
likely drivers of response of Roche anti-
PDL1 in bladder cancer.**

Roche has suggested that other companies have thus far failed to elicit strong responses with their PD1 targeted agents in this undisclosed cancer type. While a mechanistic explanation is possible, we suspect patient selection and prior BCG exposure is a more likely suggestion, assuming the undisclosed target is indeed bladder cancer.

Figure 17. Advanced Bladder cancer is a potential \$4bn sales opportunity

	US	EU-5
Incidence of bladder cancer	72,570	77,963
% distribution by grading		
<i>% in-situ</i>	50%	50%
<i>% localized</i>	30%	30%
<i>% regional / distant</i>	20%	20%
Eligible patient population	21,800	23,400
<i>pts with localized disease with a relapse</i>	7,300	7,800
<i>pts with regional/distant disease</i>	14,500	15,600
Per Patient Treatment Cost (\$)	120,000	72,000
Annual Sales (\$m)	2,616	1,685
<i>pts with localized disease with a relapse</i>	876	562
<i>pts with regional/distant disease</i>	1,740	1,123

Source: Citi Research, Cancer.gov, European Journal of Cancer 49 (2013) 1374–1403

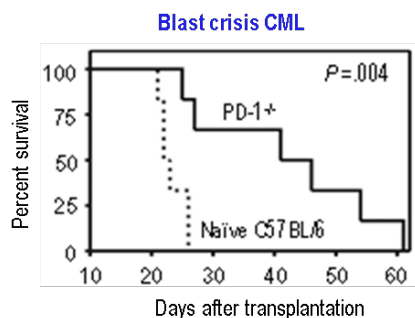
Potential role for Immunotherapy/PDL1 in Hematologic Indications

We see a significant role for immunotherapy (esp PD1 agents) in multiple blood cancers including myeloma, CML and DLBCL. We see potential risk to chronic oral cancer therapies. First data from Roche anticipated in 1H 2014.

Use of chronic oral multiple myeloma therapies are potentially at risk from integration of immunotherapy into regimens designed to achieve treatment free remissions.

Anti-PD1 therapy in CML may allow the majority of patients to enter treatment free remission, curtailing treatment durations with existing treatment

Figure 18. Mice models show that absence of PD-1 leads to a marked improvement in survival in CML



Source: Mumprecht S et al. Blood 2009;114:1528-1536, Citi Research

While there is thus far a paucity of clinical data for immunotherapy in blood cancers, we are very optimistic that immunotherapy, most notably anti-PDL1/PD1 near term will have significant treatment effects in many common blood cancers. We review the preclinical data below and eagerly await the first clinical validation of a treatment effect in Roche's soon to be completed trials of its anti-PDL1 in multiple myeloma (April 2014) as well as Pfizer and BMY's anti-CD137 (data expected 2H 2014/2015).

1. **High potential for PD1 in Multiple Myeloma.** Growth of myeloma cells is completely suppressed in PD-1 deficient mice and can be inhibited in normal mice by an anti-PD1 antibody. The combination of a anti-PD1 antibody with irradiation eliminated murine myeloma. Depletion of CD4+ and CD8+ T cells completed eliminated the anti-tumour effects of PD1/PDL1 blockade. Intriguingly, Revlimid was associated with a down regulation of both PD1 receptors and ligands supportive of the likely critical role of PD1 in myeloma. BMY, Merck, Roche all have ongoing clinical trial programs in multiple myeloma with respective PD1/ PDL1 targeted agents with first data expected March 2014 (Roche). A longer term goal for immunotherapy in the PD1 setting is set to achieve functional cure without the need for chronic therapy, with or without transplantation. **We estimate that the Myeloma opportunity for anti-PD1 agents is potentially \$1-2bn pa.**

Potential losers: Celgene's Revlimid, Pomalyst, Takeda's Velcade and Amgen's Kyprolis

2. **Functional Cure Goal in CML(Chronic Myeloid Leukaemia) for PD1.** T cell exhaustion has been implicated as a therapeutic target in non-responsive patients supporting the potential use of PD1 targeted agents. The addition of interferon to Gleevec, prior to discontinuation, has led to enhanced functional cure rates. The combination of anti-PD1 to Sprycel shown in Figure 18 looks synergistic and impressive. BMY has a combination trial with Sprycel and nivolumab underway with data expected in 2016 offering the tantalizing potential of getting the majority of patients to functional cure with <3 years of therapy. **We estimate that the potential CML opportunity is \$1bn pa for PD1 agents.**

Potential losers: Novartis's Tasigna, BMY's Sprycel, PFE's Bosilif

3. **Potential in DLBCL and Hodgkin's Lymphoma.** The utility of PD1 therapy in untreated NHL is unclear. The PD-L1 opportunity in NHL is likely confined to a subset of diffuse large B-cell lymphomas (DLBCL) with activated B-cell features (24% of primary DLBCL). The administration of anti-PD-L1 blocking antibody boosted the T cell proliferation and IFN- γ secretion in DLBCL and ALCL models only, resulting in enhanced secretion of several inflammatory cytokines. The potential role of PD1 therapy in the less common Hodgkin's Lymphoma segment looks much greater given the up regulation in the Hodgkin cells. PD1 blockade in patients restores IFN- γ consistent with T-cell exhaustion being an important target for treatment. **We calculate that the addressable PD1 population is \$1bn for DLBCL subgroup and Hodgkins combined**

Potential Losers: Roche Rituxan (maintenance).

Multiple reasons for an incompetent
immune response in CLL, going beyond
PD-1

4. **CLL — only part of the solution.** CD8+ and CD4+ T cells from CLL patients had increased expression of exhaustion markers including PD1. CLL CD8+ T cells showed functional defects in proliferation and cytotoxicity. However unlike other setting these CD8 T cells increased (not decreased) their production of interferon- γ and TNF α and IL2 suggesting the patient's incompetent immune response is likely mediated by mechanisms in addition to PD1 signaling.

Potential Losers: JNJ/Pharmacyclics Imbruvica, Gilead's idelasib

Immunotherapy Gets Personal - Diagnostics

New immune assays set to accelerate & minimize development risk

Diagnostic assays to accelerate development, optimize treatments. We anticipate that the emergence of novel immune assays based around MHC (such as the Immunoscore) and PCR (such as Adaptive biotech's QuanTILfy or ImmunID's ImmunTraCkeR) will transform the development and utilization of immunotherapeutic combinations. The critical future roles for immunodiagnostics are outlined below.

1. **Accurate risk and prognostic determination.** Figure 19 and Figure 20 shows the remarkable predictive correlation between immune activity in the tumour microenvironment (measured by way of the Immunoscore) and prognosis. We see strong parallels with the OncotypeDX assay used to identify high risk stage stage I/II metastatic breast cancer patients who may benefit from adjuvant chemotherapy.

Figure 19. The Immunoscore (a marker of CD8+ T cell infiltrate in the tumour micro-environment) at baseline is the strongest individual prognostic indicator across multiple indications, including CRC.

COX analysis for DPS	HR	Log Rank P-Values
Tumor (T) stage	1.24	0.29
N Stage	1.31	0.17
Gender	1.47	0.18
Number of total Lymph nodes	1.13	0.68
Histological grade	0.69	0.29
Mucinous Colloide	1.29	0.47
Occlusion	1.03	0.94
Perforation	4.03	0.0084
Immunoscore	0.65	0.0003

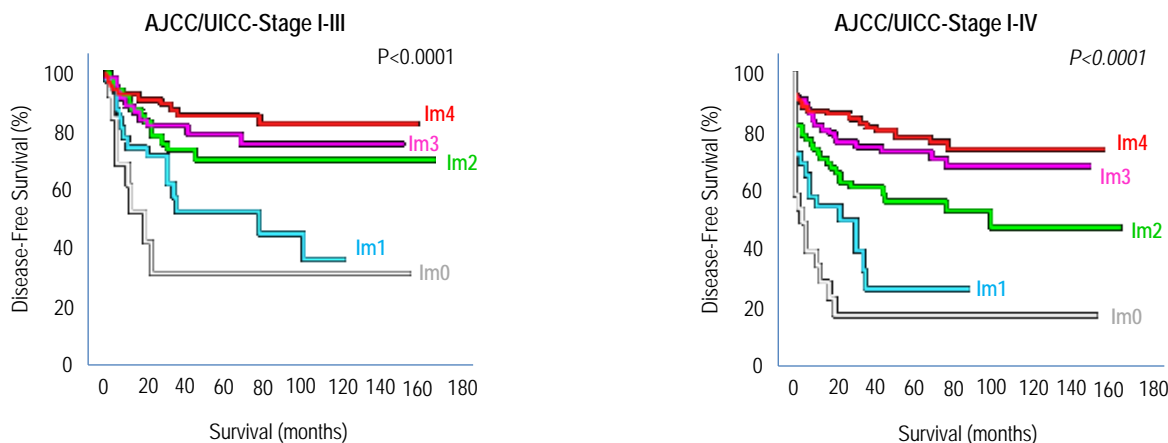
Figure 20. T cell infiltrate scoring is a much better predictive market of DFS, DSS and overall survival compared with TNM staging.

Cox Analysis	DFS		OS		DSS	
	HR	P-value	HR	P-value	HR	P-value
AJCC/UICC-TNM	1.38	0.09 ns	1.18	0.29 ns	1.43	0.10 ns
Immunoscore	0.64	<0.0001	0.71	<0.0001	0.63	<0.0001

Source: Citi Research, Mlecnik et al. J Clin Oncol 2011

2. **Optimized patient selection for efficacy.** Selection of patients with a T-cell infiltrate at the tumour micro-environment at baseline will significantly enhance the probability of positive trial outcomes. The percentages with, and without, baseline T cell infiltrate will likely differ across indications and will have different outcomes as illustrated in Figure 21

Figure 21. Prolonged survival in patients with high Immunoscore (Im) in patients with CRC



Source: Citi Research, Mlecnik et al. *J Clin Oncol* 2011

Predictive immuno-assays can lead to development of optimized rational immunotherapeutic combination regimens that is tailored for each patient

- 3. Minimizing immune related adverse events.** Immunoassays can identify patients with elevated risk of immune-associated adverse events following immune therapy. Early identification can mitigate risk through better patient selection and/or early intervention through active monitoring.
- 4. Rational development of immunotherapy combinations.** Characterization of the tumour micro-environment allows rational combinations of immunotherapeutic options to be tested (checkpoint blockers + chemokine inhibitors etc.).
- 5. The optimization of immunotherapeutic management during a patient's disease.** Treatment progressions can likely be managed through dynamic adjustment of IT based on sequential assays of the tumour micro-environment during the patient's disease. We see parallels with HIV where CD4 T cell levels are used to modify ongoing HIV treatment.

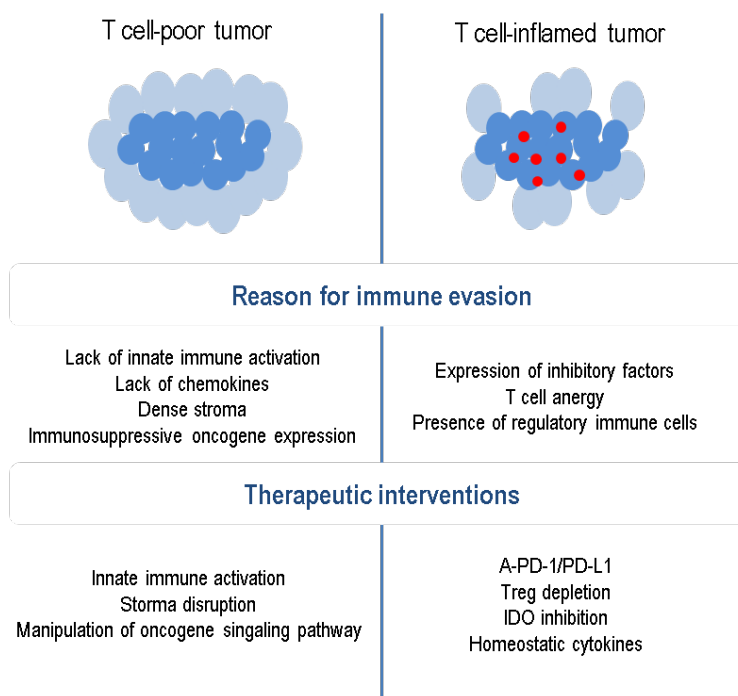
Chronic management of Stage IV cancer patients will require active management to tailor optimal immunotherapy strategies. Use of PD1s in a maintenance setting likely limited by the toxicity.

We anticipate that chronic management of stage IV patients will require ongoing management of a likely dynamic tumour microenvironment. Repeated tumour tissue biopsies to assay ligand expression, chemokine and T cell profiling will dictate optimal immunotherapy strategies to manage patients with stage IV disease experiencing recurrence. We believe that the toxicities of long term PD1 blockade will likely limit their use in a maintenance setting.

Immunotherapy for Patients with Poorly Immunogenic Cancers

The full realization of the new paradigm for cancer requires oncologists to have the ability to transform a poorly immunogenic tumour at baseline into one that has a profound treatment response to immunotherapy. We review the extent of the challenge, potential mechanisms underpinning low immunogenicity, and the emergent diverse approaches to successfully overcome them.

Figure 22. Tumours can be characterized into T cell rich (immunogenic) and T cell poor (non-immunogenic)



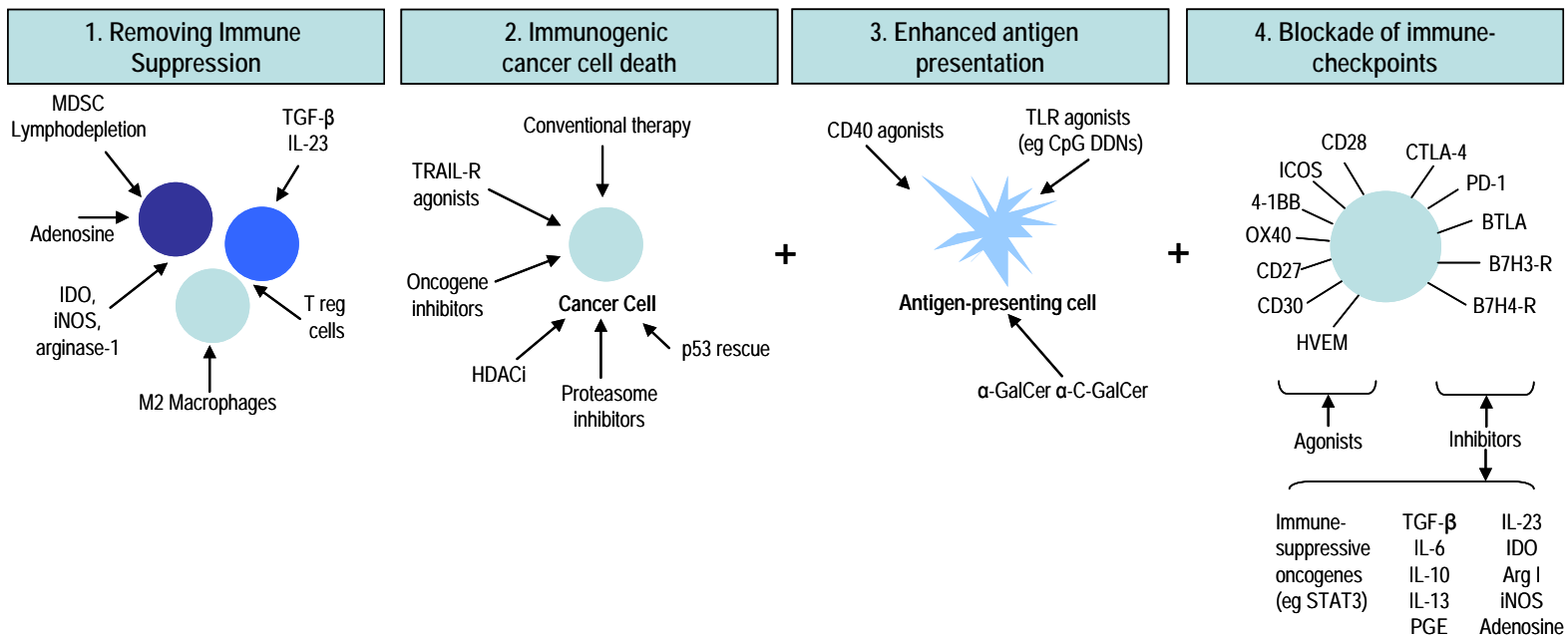
Source: Citi Research, Current Opinion in Immunology 2013, 25:268-276

We estimate that c.50% of patients with “immunogenic tumours” and c.80% of patients with “non-immunogenic tumours” will not have a TIL infiltrate at the tumour microenvironment at either baseline or even after treatment with a PD1 mediated therapy. Figure 22 shows the assorted known mechanisms through which tumours are likely resistant to immunotherapy. These include cancer antigen presentation, priming, T cell trafficking, infiltration, recognition of cancer by T cells. We anticipate the biological characterization of non-responders to improve with greater assay specificity.

There are a variety of potential mechanisms to prime a tumour prior to checkpoint therapy. These include:

- i) immunogenic chemotherapy
- ii) selective TKI (tyrosine kinase inhibitors- small molecules such as Novartis's Gleevec or Roche's Zelboraf)
- iii) epigenetic modification through HDAC inhibitors and hypo-methylating agents
- iv) therapeutic cancer vaccines, with or without adjuvants
- v) direct mediators of the innate immune system including IFN type I based therapy, other cytokines and novel targets such as STING.

Figure 23. Immunotherapy combinations can be assembled from four buckets



Source: Citi Research

Potentiation of the Immune System

We see therapeutic vaccine combinations with checkpoints agents as an exciting future therapeutic option with clinical data set to emerge over the next 3 years. The innate immune system can be potentiated in a variety of ways including.

Potential options to enhance antigen presentation include vaccines, radiotherapy, epigenetic therapy, chemo, small molecules and antibodies

Chemotherapy potentiation – There is preclinical evidence for chemotherapeutic priming in NSCLC. Earlier lines of therapy increase immunogenic stress, induce epitope spreading and reliance on PD1 signaling resulting in higher response rates for PD1 agents in second and third lines of therapy compared with treatment naive patients. Several chemotherapies such as oxaliplatin and anthracycline have been characterized as triggering immunogenic cell death. However, so called “non-immunogenic” chemotherapy (such as widely used cisplatin) could increase tumour immunogenicity through indirect mechanisms.

Epigenetic potentiation . Preclinical and clinical experience with nivolumab has shown an increase response rate for patients pre-treated with HDAC inhibitor (Syndax’s entinostat) and a hypomethylating agent (Vidaza) agents in combination prior to anti-PD1 therapy. A phase 120 patient II clinical trial for the regimen is currently underway and scheduled to report in January 2015

Radiotherapy. Prior radiotherapy is thought to exert an enhancement of immunotherapeutic response through at least two mechanism (i) priming through ATPase related cell death and subsequent epitope spreading (ii) elimination of Tregs in the tumour environment. A positive benefit of immunotherapy has been seen with both checkpoints and vaccines in clinical development.

Selective small molecule (TKI) potentiation. Alk and BCR-abl inhibitors such as Xalkori (PFE) and Gleevec/Tasigna (NOVN), Sprycel (BMJ) and BRAF inhibitor Zelboraf (Roche) are known to trigger immunogenic cell death. Conversely, EGFR inhibitors such as Tarceva are known to be immunosuppressive.

Antibody driven therapies can potentiate immunotherapy both through direct cell death (such as Herceptin) as well as through triggering ADCC (antibody dependant cytotoxicity) and activating the innate immune system through binding NK cells to the Fc receptor on the monoclonal antibody. The immunogenicity achieved through monoclonal administration is likely heightened through the emergence of antibody-dependent cell-mediated cytotoxicity (ADCC) which is likely to increase immunogenic cell death. Separately, we anticipate industry will seek to create immunoconjugates of the inhibitory checkpoint agents to enhance efficacy.

Vaccine induction. Vaccines coupled with toll like receptor adjuvants are perhaps the most potent mechanism to trigger and immune response through activation of the Innate immune system. Recent promising data include the Ph2 Aduro Biotech GVAX/CRS-207 vaccine data in pancreatic cancer where OS was increased to 6.1 months (vs 3.9 months for pts receiving GVAX alone, HR=0.54, p=0.011) with the use of two vaccines in the absence of any checkpoint background. Aduro has an interesting separate platform targeting activation of the STING receptor which plays a key role in activating the innate immune system.

Cell based therapy and bispecific TCR are options for truly refractory patients

Cell based therapy and bispecific TCR are options for truly refractory patients

For those patients where combination therapy with any of the aforementioned modalities is insufficient to precipitate an immune response, we envisage cell based approaches (CART, TCR and TIL) as being attractive options given the ability to effectively circumnavigate. We have extensively described several of these programs now in clinical development in our report on Novartis' CART-19 ([Blockbuster #2: CART- Weapons of Mass Cancer Destruction](#)).

The bespoke nature of these agents, manufacturing and logistical challenges are likely to keep this option the preserve of the refractory patient. Since the publication of our Novartis report, we note the emergence of cell based immunotherapy from Adaptimmune (TCR), Juno (TCR), Kite (TIL), Lion among others. Novartis remains the only multinational to have licensed the technology to date, but we anticipate other companies to follow in the near future.

Prior lines of therapy in NSCLC may increase responsiveness to anti-PD1 mediated immunotherapy

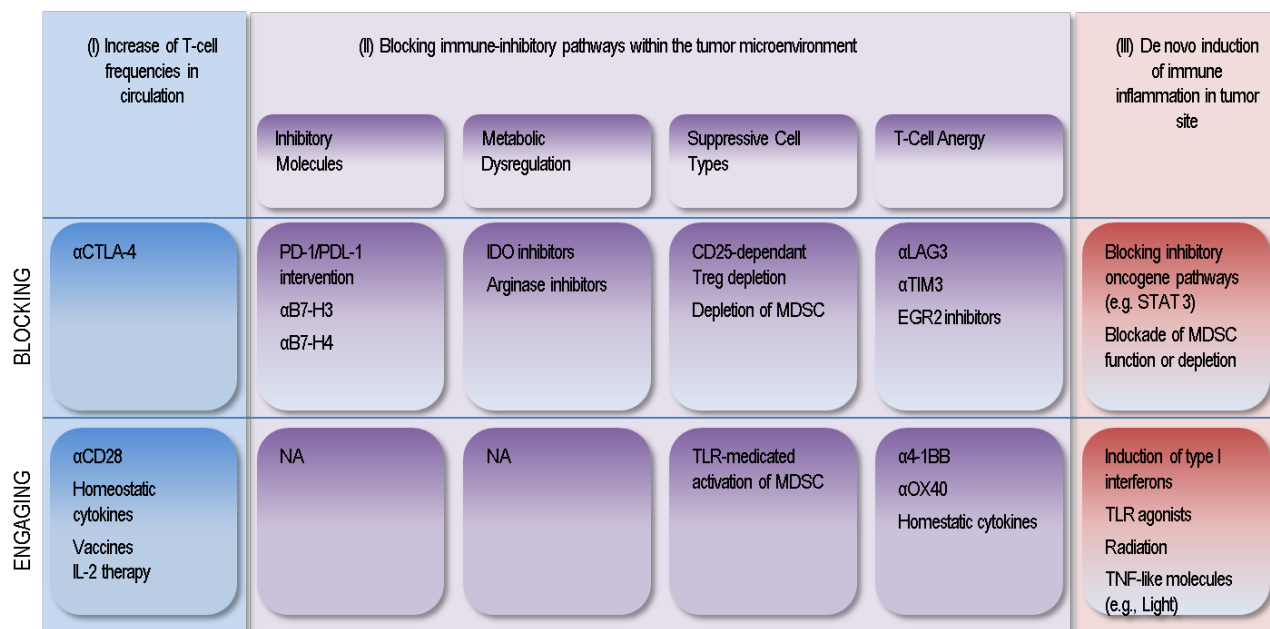
Figure 24. Prior lines of treatment in NSCLC is associated with a higher ORR with anti-PD1 therapy. We suspect increased PD1 expression in pts having received prior therapy.

Subgroup	ORR, % (n/N) [95% CI]*
Age	
<70 yr	17 (15/90) [9.6, 26.0]
≥70 yr	18 (7/39) [7.5, 33.5]
Sex	
Female	18 (9/50) [8.6, 31.4]
Male	16 (13/79) [9.1, 26.5]
ECOG performance status	
0	11 (3/27) [2.4, 29.2]
1-2	19 (19/102) [11.6, 27.6]
Histology	
Squamous	17 (9/54) [7.9, 29.3]
Non-Squamous	18 (15/74) [9.7, 28.2]
Prior therapies	
<3	12 (7/59) [4.9, 22.9]
≥3	21 (15/70) [12.5, 32.9]
Prior TKI therapy	
Yes	11 (4/36) [3.1, 26.1]
No	19 (18/93) [11.9, 28.9]
EGFR Status	
Mutant	17 (2/12) [2.1, 48.4]
Wild-type	20 (11/56) [10.2, 32.4]
Unknown	15 (9/61) [7.0, 26.2]
KRAS status	
Mutant	14 (3/21) [3.0, 36.3]
Wild-type	25 (9/36) [12.1, 42.2]
Unknown	14 (10/72) [6.9, 24.1]

Confidence intervals for ORRs were calculated using the Clopper-Pearson method

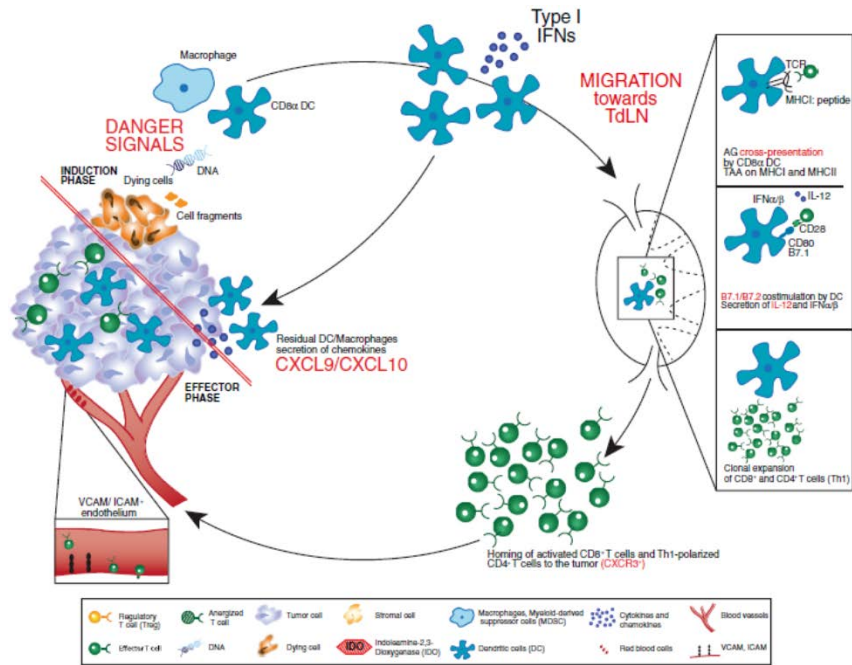
Source: Citi Research, Gettinger et al. IASLC, 2013

Figure 25. We see three key categories for triggering and optimizing immune response in metastatic disease.



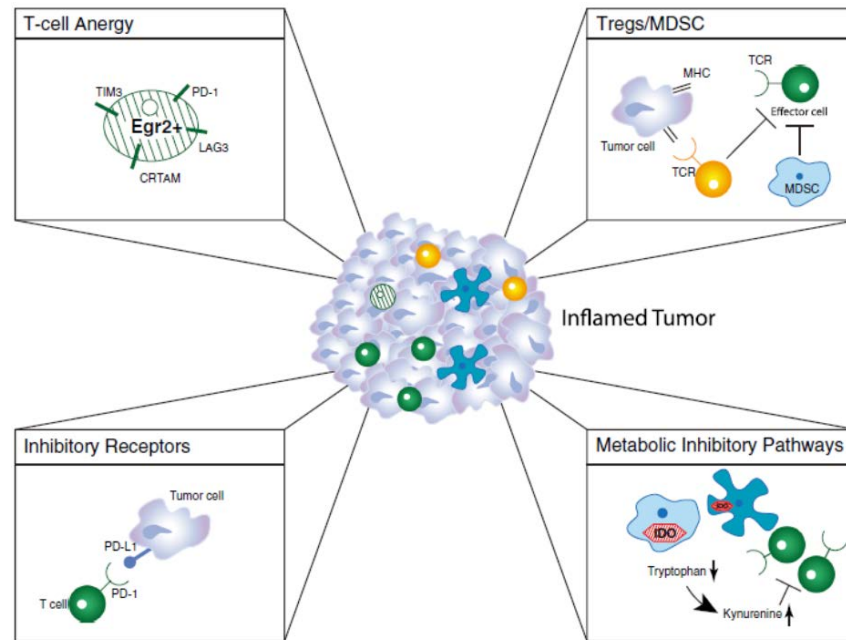
Source: Citi Research, Spranger and Gajewski Journal for Immunotherapy of Cancer 2013, 1:16 <http://www.immunotherapyofcancer.org/content/1/1/16>

Figure 26. Processes involved in an anti-tumour immune response resulting in a tumour with an “inflamed” immunophenotype



Source: Citi Research and Spranger and Gajewski Journal for ImmunoTherapy of Cancer 2013, 1:16
<http://www.immunotherapyofcancer.org/content/1/1/16>

Figure 27. Dominant inhibitory mechanisms in the tumour microenvironment that suppress anti-tumour immunity



Source: Citi Research and Spranger and Gajewski Journal for ImmunoTherapy of Cancer 2013, 1:16
<http://www.immunotherapyofcancer.org/content/1/1/16>

Chemokine Inhibitors- the Next Blockbusters Class

We expect chemokine inhibitors to emerge as the next class of immunotherapy- CCR5i and CXCR4i are among the most promising agents

Strong scientific rationale backing therapeutic synergies for a combination of CCR5 inhibitor and an anti-PD1.

MRK, BMY, PFE and INCB all have CCR2 or CCR2/5 inhibitors.

CXCR4 axis is potentially another area of interest. Sanofi recently received approval for CXCR4 inhibitor Mozobil, but plans for further development unknown.

We anticipate the interest in the chemokine modulation field to intensify in 2014. We anticipate positive phase I data from the ongoing trial (MARACON) with PFE's maraviroc (Selzentry) in stage IV colorectal cancer patients with liver metastases pre-selected for a baseline inflammatory tumour micro-environment.

Among other activities, CD8+ T effector cells at the tumour margin secrete mitogenic CCR5 increasing tumour growth by binding to CCR5 receptors on malignant cells. Blockade with CCR5 inhibitors in animal models has induced partial responses with minimal toxicity, we believe. We anticipate that the partial responses reflect the inhibitory activity of CCR5 blockade on T-reg activity through TGF β blockade. Resistance of CCR5 is partly determined, we believe, by up regulated PDL1 expression on cancer cells. The therapeutic combination of a CCR5 inhibitor and an anti-PD1 is therefore obviously appealing. Critically the scheduling of CCR5 is important given the role of CCR5 in facilitating T cell migration to the tumour micro-environment (also exemplified in Graft Versus Host Disease or GVHD)

As we have previously described ([Merck's NEXT Cancer Immunotherapy. Old Dog, New Tricks](#)), MRK, BMY, PFE and Incyte all have CCR5 or CCR2/CCR5 inhibitors in clinical development. Both Selzentry (PFE) and vicriviroc (MRK) have been shown to be safe and well tolerated when administered in HIV. We therefore expect the sponsor companies to quickly initiate phase I/II combinations trials in 2014 post positive MARACON data.

Additional chemokine targets include CXCR4 axis, both the CXCL12 ligand and the CXCR4 receptor. Recently published data in pancreatic cancer models demonstrated how CXCR4 blockade materially increases T cell density at the tumour site and shows considerable synergy with PD1 and CTLA4 blockade. CXCL12 was principally secreted by the FAP+ve fibroblasts in the tumour stroma, binding to CXCR4 receptors expressed. The immunosuppressive mechanism of action of CXCL12/CXCR4 axis is unknown. We note that Sanofi has attained approval for plerixifor (Mozobil), a CXCR4 receptor inhibitor, in NHL and MM in combination with G-CSF but we are unaware of Sanofi's plans to explore this further in a clinical setting. We note other CXCR4 agents in late state pre-clinical and early clinical development including BMY's anti-CXCR4 antibody.

Figure 28. Up-regulation of chemokines in the tumour micro-environment is ubiquitous in the majority of solid tumours

	T _H 1	Chemokines			Cytotoxic	Adhesion	References
	STAT-1	CXCR3/CSCL9-11 Pathway	CCR5/CCL3-5 Pathway	Granzyme Perforin			
	IRF-1/IFN-γ-SG Pathway			Granulysin/TIA-1/CASPs Pathway	Adhesion Molecules		
Prognostic							
Breast	+	+		+	+	Ascierto et al., 2012	
	+	+	+			Curtis et al., 2012	
Ovarian	+		+	+		Leffers et al., 2010	
	+	+			+	Zhang et al., 2003	
Melanoma	+	+	+			Messina et al., 2013	
	+	+				Mann et al., 2010	
Colorectal	+	+	+	+	+	Mlecnik et al., 2010	
	+			+		Galon et al. 2006	
	+			+		Pages et al., 2005	
	+		+	+		Tosolini et al., 2011	
		+				Jiang et al., 2010	
Lung			+			Moran et al., 2002	
Hepatocellular	+	+	+		+	Chew et al. 2012	
	+		+	+	+	Chew et al. 2010	
Predictive							
Breast (Chemo)		+				Denkert et al., 2010	
	+	+				Desmedt et al., 2008	
	+	+				Teschendorff et al., 2007	
	+	+				Ignatiadia et al., 2012	
Melanoma IL-2/ vaccine/adoptive therapy/anti CTLA-4)	+		+		+	Wang et al., 2002	
	+					Weiss et al., 2011	
	+	+				Gajewski et al., 2010	
	+	+	+			Bedognetti et al., 2012	
	+	+	+	+		Ji et al., 2012	
	+	+	+	+		Ulloa-Montoya et al., 2013	
Lung	+	+	+	+		Ulloa-Montoya et al., 2013	
Mechanistic							
Melanoma (IL-2/vaccine anti-CTLA-4)						Panelli et al., 2002	
						Wang et al., 2002	
						Weiss et al., 2011	
						Aarntzen et al., 2012	
						Ji et al., 2012	
Basal Cell (Imiquimod)	+	+	+			Panelli et al., 2007	

Source: Citi Research, Immunity 39, July 25 2013, Elsevier Inc.

Therapeutic Vaccines on the Cusp of Clinical Validation

The utility of multiple cancer vaccines set to be validated in next 3 years. We remain very optimistic- impressed with Aduro and Inovio approaches among others.

Cancer vaccines have thus far failed to demonstrate efficacy compared with checkpoints, bi-specific antibodies or cell based therapies. We anticipate that patient selection strategies, superior antigens and combination based approaches will translate into the approval and widespread adoption of a broad range of therapeutic cancer vaccines. Near term, we discuss the potential for GSK's soon-to-be-concluded Ph3 MAGE-A3 program in lung and skin cancer to translate into an approved product.

Both GSK and Merck Serono are exploring their peptide vaccines based on patient selection after initial disappointing data in an unselected patient population. While we remain cautious on Merck Serono's Stimuvax Ph3 outcome (*details available on request*), we maintain a modicum of optimism for the prospect for GSK's MAGE-A3 in gene signature positive lung cancer and melanoma, despite the apparent absence of antigen specific CD8 T cells. We do not anticipate gene signature data to be made public until late 2014/ early 2015.

Very encouraging data from Aduro's pancreatic cancer vaccine validates utility of cancer vaccines. Positive for the potential for other vaccine targets.

Recent Aduro data very encouraging proof of concept for cancer vaccines. Recent positive phase II vaccine data phase II from Aduro and Celldex indicate that we are close to establish proof of concept for systemically administered therapeutic cancer vaccines. Aduro's randomized, controlled, multi-center study phase II 93 patient phase II trial showed a statistically significant survival benefit in patients receiving the combination of GVAX Pancreas and CRS-207 cancer vaccines (Arm A) compared to GVAX Pancreas vaccine alone (Arm B). The median overall survival of the patients receiving the combination was 6.1 months compared to 3.9 months for those receiving GVAX monotherapy (HR=0.54, one-sided p=0.011). One-year survival probability for patients in Arm A was 24% compared with 12% for patients in Arm B. We see similar encouraging approaches for therapeutic cancer vaccines from the likes of Inovio and Immatix (albeit with very different technologies), both partnered with Roche.

Combination of therapeutic vaccines with anti-PD1 way forward for optimizing activity of innate immune system.

We remain most excited by the potential for the combination of vaccines with checkpoint inhibitors, such as PD1 antagonists to optimize the activity of the innate immune system. We anticipate Roche to begin combination vaccine trials with their anti-PDL1 as early as 2014

GSK MAGE-A3: Positive Surprise or Misplaced Optimism?

MAGE-A3's innovative trial design allows GSK to refine patient selection based on identification of a tumour gene signature that is likely a marker for a patient with an immunogenic tumour.

GSK had access to unblinded data from the phase III DERMA trial, we believe.

Absence of MAGE-A3 CD8+ T cells is very problematic.

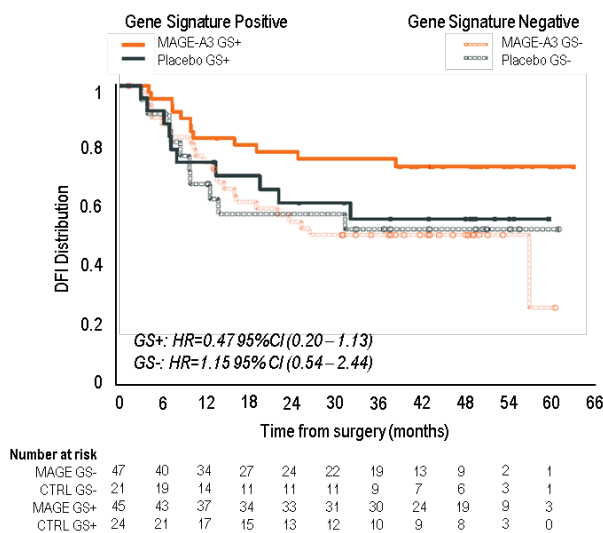
While GSK's senior management continues to be non-committal over the ongoing MAGE-A3 program, we were struck by the conviction of senior GSK MAGE-A3 scientists following their recent presentation on the MAGE-A3 program at SITC in November 2013, only two months following the failure of DERMA to reach its primary end point in melanoma. We understand that as part of the trial design, GSK has seen un-blinded data from c.30% of the gene signature positive patients in the phase III DERMA trial as part of the predefined gene signature "training set".

Post hoc editing of gene signature could translate into a false positive signal. We believe that GSK's access to un-blinded data from part of the recently concluded MAGE-A3 phase III DERMA trial (melanoma) is one potential explanation for our observation of continued optimism among GSK's MAGE-A3 senior scientists. However, we caution that any positive efficacy signal observed in the un-blinded gene signature positive DERMA patients could result from post hoc "editing" of the gene signature, rather than confirm a real treatment benefit. Our forecasts for £197m in 2020e continue to reflect our conservative stance

Does the science support efficacy for GSK's MAGE-A3? We continue to struggle with reconciling a potential treatment effect with MAGE-A3 with the absence of MAGE-A3 specific CD8 T cells. We are unconvinced that the increased levels of MAGE-A3 specific CD4 and B cells contribute to efficacy. We discuss the potential scientific and trial design issues extensively in the report and discuss our relative confidence levels for each of the outstanding three primary end-points.

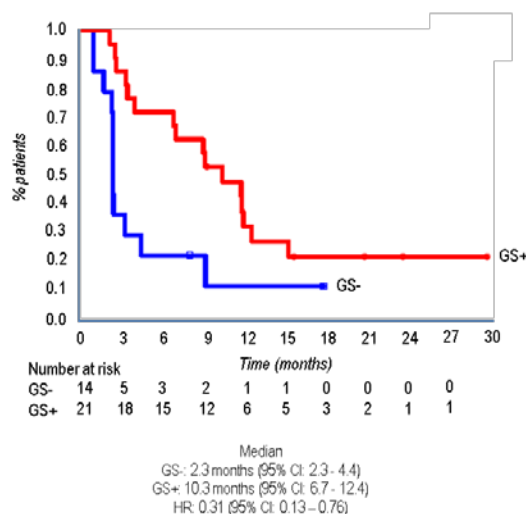
GSK's highly innovative trial design for the MAGE-A3 program has allowed GSK to both select and refine patient selection based on tumour gene signature. The 84-gene signature correlates well with the pro-inflammatory phenotype described in the previous section (see: Immunotherapy for (almost) all). We anticipate that these patients have a heavy T cell infiltrate around the site of the metastasis suggesting immunogenic disease.

Figure 29. Biomarkers in NSCLC: impact of predictive gene signature on the Disease-Free Interval.



Source: Citi Research, Louahed et al., EORTC-NCI-AACR 2009

Figure 30. Ph2 gene signature+ pts experienced a greater treatment benefit with GSK MAGEA3 compared with GS- pts in melanoma.



Source: Citi Research, Louahed et al, ASCO 2008

Figure 31. GSK's 33 gene signature used in MAGE-A3 trials addresses many genes intrinsically involved in innate/adaptive immune response.

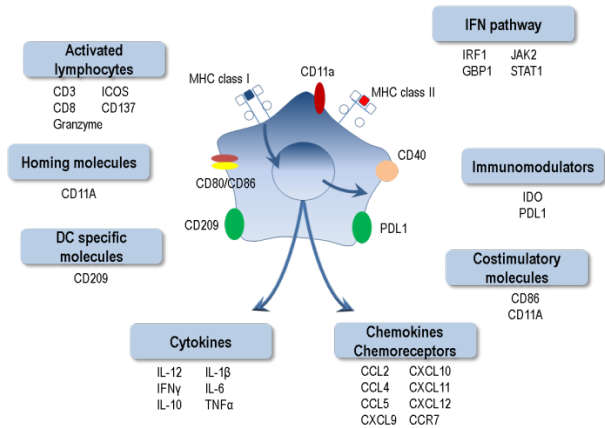


Figure 32. MAGE-A3 antigen is expressed in multiple tumours and never in tumour tissues

Tumor Type	MAGE-A3 expression
Lung cancer	35%
Bladder	41%
Oesophagus	46%
Liver	48%
Gastric	48%
Head and Neck	49%
Multiple Myeloma	60%
Melanoma	65%
Normal cells	0%*

* Except in Testis: expression 100% but no antigen presentation capabilities

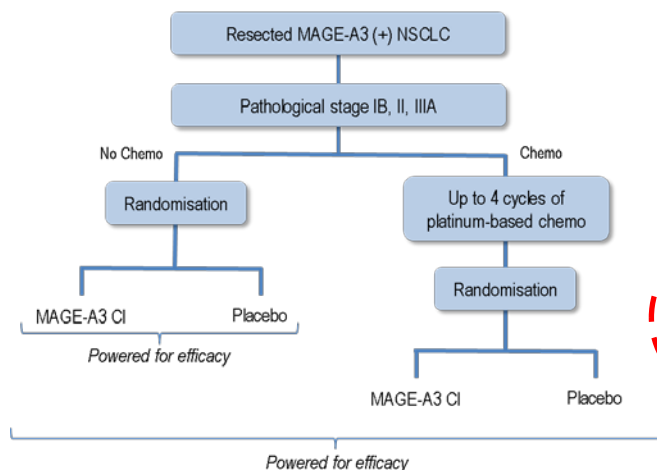
Source: Citi Research and Ulloa-Montoya. 2013 J Clin Oncol 2388-2395

Source: Citi Research and Company data

GSK has access to unblinded data from DERMA trial from the gene signature positive patients.

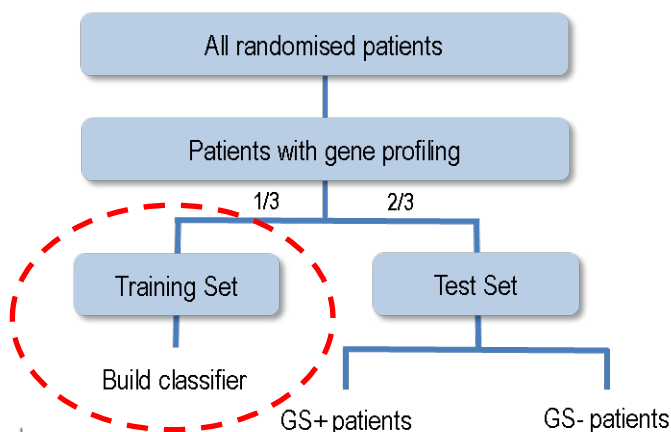
Our understanding is that the gene signature used in the phase III melanoma program was very similar to that assessed in the phase II trials. The revalidation of the market in the ongoing phase III reflects both the shift to formalin fixed tissues as well as a PCR based assay for the gene signature.

Figure 33. MAGRIT lung cancer trial: study design.



Source: Citi Research, Company data

Figure 34. GSK has access to the unblinded melanoma dataset in the gene signature positive subgroup.



Source: Citi Research, Company data

We expect overall data from MAGRIT lung cancer trial to show no benefit for MAGE-A3 (data in 1Q 2014), but we expect the gene signature positive subgroups to show a positive benefit (data expected late 2014/early 2015).

While we continue to expect that MAGRIT overall data will show no benefit for the vaccine, we acknowledge that the prospects for a positive benefit in the overall NSCLC indication is arguably higher than with the (failed) DERMA melanoma trial. We anticipate headline data from the MAGRIT lung cancer trial in 1Q 2014.

1. Unlike DERMA, the MAGRIT patient population (stage IB, II and IIIA) is identical to that used in the positive phase II trial.
2. The phase III MAGRIT trial used the more potent AS15 adjuvant compared with the AS02 used in the phase II program.
3. The stratification for cisplatin therapy (up to 4 cycles) may increase the responsiveness of the chemo treated patients to MAGE vaccination. While cisplatin has been shown not to trigger immunogenic cell death directly, it will invariably trigger epitope spreading and thus could potentiate dendritic cell processing in response to MAGE-A3 vaccination.

Disease Free Survival in the Pre-Defined Gene Signature Patient Population is the second co-primary endpoint in both DERMA and MAGRIT

GSK's best hope remains gene signature subgroups: but probability still low

While we believe that the pre-defined gene signature will likely select for patients with more immune-responsive cancers, we are unconvinced that GSK's AS15 adjuvated MAGE-A3 vaccine will translate into a large enough clinical benefit for reasons outlined in the following section

Key Concerns For GSK's MAGE-A3 program

The inability to detect an antigen specific CD8+ T cell response to MAGE-A3 vaccination is our greatest concern.

Absence of CD8+ T cell response. Our pivotal historic concern with GSK's MAGE-A3 program has been the lack of detectable antigen specific CD8 T cells following vaccination. There is, we note, a significant increase in monoclonal antibody and CD4+ response to vaccination. While there is an increase in monoclonal antibody levels to MAGE-A3 in response to the vaccine, historic data over the importance of a B-cell response has been underwhelming (see Canvax). Any efficacy thesis needs to be based on lymph node sequestering of CD8 cells or invoking cytotoxic CD4 cells.

Gene signature biasing in melanoma development. Our understanding is that the gene signature developed in the phase II trial was based on cutaneous rather than visceral biopsies. This brings into doubt the relevance of this gene signature as it relates to patients with non cutaneous sites of disease recurrence. More positively, we understand that the lung gene signature was developed on the basis of mediastinal metastatic biopsies.

Immunosuppressive T-reg cells likely minimize the therapeutic efficacy of MAGE based vaccination. Recent publications have highlighted the increase in antigen specific T-regs in response to MAGE A3 vaccination. We anticipate the involvement of T-regs is much reduced in the ongoing DERMA and MAGRIT programs giving the adjuvant settings being explored.

MAGE-A3 heterogeneity. An important concern is the heterogeneity of MAGE A3 expression in the neoplastic cells. We are paradoxically reassured that the phase II data showed that the patients who progressed post MAGE-A3 treatment had MAGE-A3 expression with their tumour recurrence.

\$6bn market potential in gene signature positive patients. Figure 35 and Figure 36 illustrate the potential market opportunity for both MAGE-A3 in lung and melanoma. We calculate a NPV of \$18bn and \$6bn respectively for NSCLC and melanoma approvals in gene signature positive patients. The high NPV reflects the significant barriers to competition given GSK's lead time and the material barriers to innovative or generic competition.

Figure 35. \$4.5bn sales opportunity in NSCLC (gene signature only)

	MAGRIT NSCLC (Stage IB, II, IIIA)
No of pts with NSCLC	516,645
US	197,045
EU	244,800
Japan	74,800
No of pts with Stage IB, II, IIIA NSCLC	199,942
US	76,256
EU	94,738
Japan	28,948
No of pts above expressing MAGE A3	99,971
US	38,128
EU	47,369
Japan	14,474
No of pts expressing both MAGE A3 and gene signature	
US	19,064
EU	23,684
Japan	7,237
Pricing (\$)	
US	120,000
EU	72,000
Japan	72,000
Sales potential (\$m) in GS+ MAGEA3+ population	4,514
US	2,288
EU	1,705
Japan	521

Source: Citi Research

Figure 36. \$1.6bn sales opportunity in Melanoma (gene signature only)

	DERMA Melanoma (Stage IIIB/C)
No of pts with melanoma	219,725
US	124,826
EU	79,782
Japan	15,117
No of pts with Stage IIIB, IIIC melanoma	49,438
US	28,086
EU	17,951
Japan	3,401
no of pts expressing MAGE A3	32,135
US	18,256
EU	11,668
Japan	2,211
no of pts expressing both MAGE A3 and gene signature	
US	9,128
EU	5,834
Japan	1,105
Pricing (\$)	
US	120,000
EU	72,000
Japan	72,000
Sales potential (\$m) in GS+ MAGEA3+ population	1,595
US	1,095
EU	420
Japan	80

Source: Citi Research

MAGE-A3 addressable patient population for NSCLC set to increase.

Recent USPSTF recommendation for annual CT scans could increase the number of high risk smokers diagnosed with earlier stages of lung cancer.

The recent recommendation by the US Preventive Services Task Force for annual CT scans for high risk smokers is likely to increase the percentage of patients diagnosed with stage I-III disease ([*Immunotherapy Opportunity In Advanced Lung Cancer Set To Shrink - Upside for Immunotherapy Sponsors is Beyond Lung Cancer*](#)). Currently only c.30% of patients with NSCLC are diagnosed with earlier than stage III/IV disease. The expansion of the addressable patient population could increase annual revenues by \$1-2bn per annum and increase the total NPV from \$24bn to \$30bn.

Potential for MAGE-A3 use outside lung cancer melanoma, either as a single agent or in combination.

Potential in other cancer indications, we well as in combination. The high levels of MAGE A3 expression in other solid tumours potentially broaden the market considerably as shown in Figure 32. We note that GSK is already exploring MAGE-A3 vaccine in MAGE-A3 positive bladder cancer (data expected in 2016). We also anticipate that GSK will explore the potential for additive clinical benefit or synergy by combining MAGE-A3 vaccine with other agents, including both small molecules (such as dabrafenib and trametenib) as well as IT (such as anti-PD1, and anti-ICOS).

Positive data with MAGE-A3 vaccine would mean a significant NPV uplift to GSK given limited competition and significant toxicity precluding use of PD-1 in adjuvant setting

We see very limited near term competition given GSK's competitive lead time with MAGE A3. In addition, the immune related adverse events associated with PD1 mediated therapies likely preclude use in lower risk adjuvant patients, in contrast to the placebo like profile of MAGE-A3. The terminal value of the MAGE-A3 (assuming positive data) is significant given the almost insurmountable barriers in generating a generic vaccine.

Glossary of Terms

Figure 37. 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 Lymphocytic 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 Administration, 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
Hematopoiesis	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 antigens on 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 naive 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 and migrated 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

Figure 38. Citi's Immunotherapy Basket, CGRBIMMU Performance Data

Citi Research Basket Name	Inception Date	Perf. Since Inception	Rel. Benchmark Perf. Since Inception	
	22-May-13	35%	25%	
Constituents	Date Added	Price Added	Price (11/02/2014)	Perf. Since Added
Amgen	22-May-13	105	120	15%
AZN	22-May-13	35	39	13%
Bristol Myers Squibb	22-May-13	46	52	12%
GSK	22-May-13	18	16	-8%
Incyte	22-May-13	22	66	197%
Merck	22-May-13	47	55	17%
Novartis	22-May-13	74	72	-2%
Roche	22-May-13	259	256	-1%

Source: Citi Research, Past performance is not indicative of future results. No transaction costs are assumed.
"Price" is market-close price on date indicated.

Companies mentioned:

Takeda Pharmaceutical (4502.T; ¥4,670; 2)
Ono Pharmaceutical (4528.T; ¥8,920; 1)
AbbVie (ABBV.N; US\$49.55; Not Rated)
Amgen Inc (AMGN.O; US\$120.30; 1)
AstraZeneca PLC (AZN.L; £39.15; 2)
Bayer AG (BAYGn.DE; €95.45; 1)
Bristol Myers Squibb (BMY.N; US\$52.12; 1)
ChemoCentryx (CCXI.O; US\$7.05; 2)
Celldex Therapeutics Inc (CLDX.OQ; US\$25.66; Not Rated)
Celgene Corp (CELG.O; US\$156.62; 1)
Compugen Ltd (CGEN.TA; NIS43.82; Not Rated)
Celldex Therapeutics Inc (CLDX.OQ; US\$25.66; Not Rated)
Gilead Sciences Inc (GILD.O; US\$80.98; 1)
GlaxoSmithKline PLC (GSK.L; £16.08; 2)
Immunovaccine Inc (IMV.V; C\$1.16; Not Rated)
Incyte Corporation (INCY.O; US\$66.13; Not Rated)
Inovio Pharmaceuticals Inc (INO.A; US\$2.73; Not Rated)
Innate Pharma SA (IPH.PA; €10.37; Not Rated)
Johnson & Johnson Inc (JNJ.N; US\$91.07; 1)
Eli Lilly (LLY.N; US\$53.97; 1)
Merck KGaA (MRCG.DE; €118.25; 2)
Merck & Co (MRK.N; US\$54.89; 2)
NewLink Genetics Corp (NLNK.OQ; US\$41.88; Not Rated)
Novartis AG (NOVN.VX; SFr72.00; 1)
Novo Nordisk A/S (NOVOB.CO; Dkr234.70; 1)
Pharmacyclics Inc (PCYC.O; US\$132.23; Not Rated)
Pfizer (PFE.N; US\$31.47; 1)
Roche Holding AG (ROG.VX; SFr254.80; 1)
Sanofi SA (SASY.PA; €71.99; 2)
Shire Pharmaceuticals (SHPL.L; £31.45; 1)

Notes

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Appendix A-1

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