BRYAN, GARNIER & CO

INDEPENDENT RESEARCH

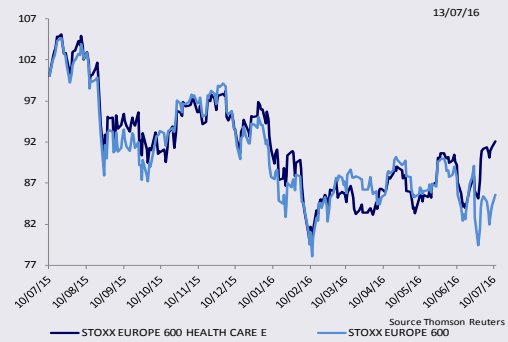
13th July 2016

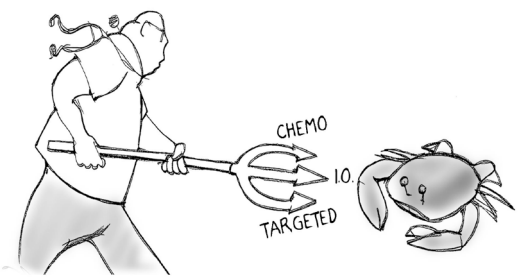
Healthcare

BG Oncology Day: the devil is in the details

Healthcare

ABLYNX		**BUY**	**FV EUR18**
Last Price	EUR12.525	*Market Cap.*	EUR762m
ASTRAZENECA		**BUY**	**FV 5370p vs. 5100p**
Last Price	4476p	*Market Cap.*	GBP56,604m
CELYAD		**NEUTRAL**	**FV EUR20**
Last Price	EUR23.635	*Market Cap.*	EUR220m
GENMAB		**BUY**	**FV DKK1600**
Last Price	DKK1202	*Market Cap.*	DKK71,920m
INNATE PHARMA		**BUY**	**FV EUR18**
Last Price	EUR11.15	*Market Cap.*	EUR600m
IPSEN		**BUY**	**FV EUR64 vs. 63**
Last Price	EUR53.3	*Market Cap.*	EUR4,437m
MORPHOSYS		**BUY**	**FV EUR62**
Last Price	EUR39.22	*Market Cap.*	EUR1,041m
NOVARTIS		**NEUTRAL**	**FV CHF89**
Last Price	CHF80.65	*Market Cap.*	CHF211,877m
ROCHE HOLDING		**BUY**	**FV CHF293**
Last Price	CHF255.5	*Market Cap.*	CHF179,505m
SANOFI		**NEUTRAL**	**FV EUR83**
Last Price	EUR74.59	*Market Cap.*	EUR96,005m
SHIRE PLC		**BUY**	**FV 6750p**
Last Price	4855p	*Market Cap.*	GBP43,641m





Immuno-oncology is both fascinating and complex. So, to help investors navigate through this, we organised a dedicated day in collaboration with Institut Curie's specialists along with two companies with a marked footprint in this field (ROG, IPH). Here are our key takeaways along with the names we deem worthy to play the field in the short term.

- There is no one-fits-all strategy. I-O molecules have generated impressive results and will continue to do so. Combination therapies are likely to reach the best outcomes, as they allow the targeting of several fronts/pathways… But evaluating tumour specificities, and especially its micro-environment, will be key to gauge and select the best agents or targets in a given indication. And against this backdrop, the development of biomarkers will increasingly become of importance.

- Do not restrict yourself to I-O! Chemo, radiation and targeted therapies will continue to play a key role in the future paradigm, due to an attractive cost and/or robust synergies with immunotherapies. In our view, IPN's cabozantinib, or PARP and BTK inhibitors (like AZN's Lynparza and acalabrutinib), are pretty good examples of these non-I-O agents with quite significant sales potentials.

- Five companies within our universe are likely to generate significant cancer-related news-flow by year-end. ROG and AZN particularly stand out among the big names with respectively, notably: 1/ the results of the APHINITY study (Perjeta/Herceptin/Chemo in adjuvant HER2+ breast cancer) in Q4, and 2/ phase III data involving acalabrutinib in relapse CLL, also expected in Q4. When it comes to smaller ones, we believe IPN, GEN and IPH are worth playing as we correspondingly expect: 1/ the European approval of "cabo" for the treatment of 2L kidney cancer in H2; 2/ daratumumab's label expansion to the 2L of myeloma, along with follow-up data at the ASH congress; 3/ and phase Ib data involving lirilumab in combination with BMS's nivolumab.

- Our AZN's FV is lifted from GBp5,100 to GBp5,370 as we now integrate "acala" into our estimates. And we raised the FV for IPN (EUR64 vs EUR63) having changed our FX assumptions.

Analyst:
Team Pharma
33(0) 1 56 68 75 33
healthcare@bryangarnier.com

Sector Analyst Team:
Mickael Chane Du
Eric Le Berrigaud
Hugo Solvet

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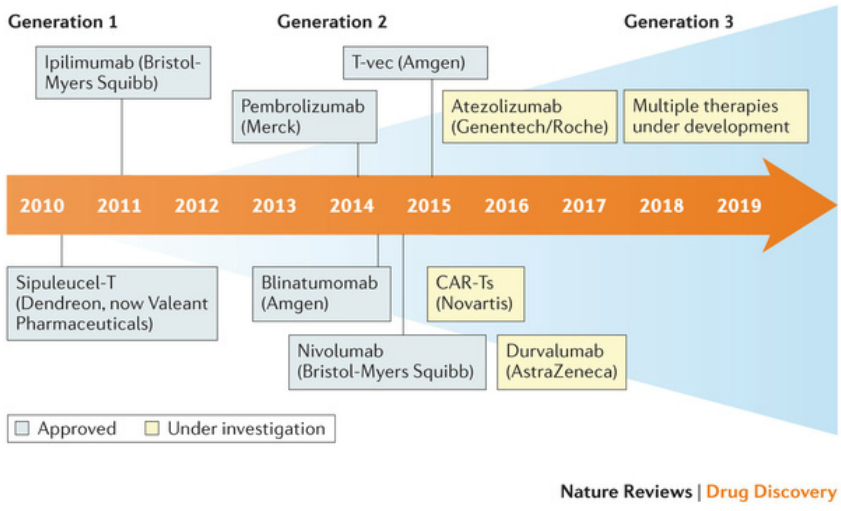
1. From oncology to immune-oncology

Immuno-oncology (I-O) has been a buzzword that refers to **all therapies mobilising the immune system to fight cancers**. But a more detailed look reveals a plethora of approaches that we can divide into two types: 1/ active immunotherapies, like cancer vaccines, which regroup the compounds that stimulate the immune system (e.g. by enhancing the presentation of tumour-associated antigens); and 2/ passive immunotherapies which are instead solutions that improve the pre-existing immune responses.

For quite a long time, the scientific community has been rather sceptical when it comes to immune-oncology (I-O) agents… Certainly because of a lack of understanding, along with the use of non-specific approaches (e.g. IL-2, TNF-α). But, notably since the regulatory approval of ipilimumab (an anti-CTLA-4 mAb), the field has been experiencing a complete renaissance… And a large variety of approaches/mechanisms of action has since emerged, including small molecules, other monoclonal antibodies, CAR-T cells and bispecific molecules.

Deeper and longer-lasting responses, and thus largely improved overall survival rates, have since then been achieved with this increasingly exhaustive I-O portfolio. But the "Holy Grail" is far from being achieved due to the extreme complexity and heterogeneity of antigens, tumour micro-environments, genomics and immune-system/cancer interrelations… And the more we know, the more complex it looks.

Fig. 1: I-O drugs since the approval of Sipuleucel-T and ipilimumab



Source: Nature

To help investors navigate through this, we decided to organise an oncology-dedicated day in collaboration with the Curie Institute with a focus on four themes: 1/ how our immune system can kill cancer cells; 2/ how Curie's translational research team works; 3/ the importance of the tumour micro-environment (TME); and, ultimately, 4/ the place of immune checkpoint blockers and bispecifics within this nascent paradigm. And after that, two companies within our coverage (ROG and IPH) presented their I-O portfolios and their respective business strategies.

2. The immune response: a complex story

Before giving our key take-aways and perchance some recommendations, we have summarised here some of the key points to retain regarding the science behind the construction of the current I-O paradigm; the objective being to answer some key questions like: (i) how an effective immune response is mounted? (ii) what is a checkpoint blocker and why such a buzz around it? (iii) what is the so-called tumour micro-environment and why is it becoming so important?

2.1. From surveillance to "prison break"

The immune system: a complex and dynamic network

The immune system has to be seen as a pretty dynamic and complex network in which many different cells, chemicals and hormones constantly interact to protect our body in the best possible way, be it against tumours or other malignancies. That said, such organisation can be subdivided into two interdependent and equally important subparts: the innate and the adaptive systems. The first one has to be seen as our very first barrier of defence; with an ability to induce rapid attacks against a wide range of invaders and send signals to the rest of the system… especially the adaptive cells – which are necessary to mount a more potent/specific response, and actually benefit from a "memory".

Fig. 2: Innate and adaptive immunity

	Innate immunity	Adaptive immunity: specificity
Examples	Dendritic cells, Natural Killer cells, macrophages	T and B cells
Development	Bone marrow then tissues	BM and thymus, then lymphoid organs
Lag phase	Immediate response	Response takes a few days
Specificity	Limited, same response mounted to a wide range of agents	High, response directed only to the agents that initiated it
Diversity	Limited, hence limited specificity	Extensive, and resulting in a wide range of antigen receptors
Memory	Absent, subsequent exposures generate the same response	Present, subsequent exposures to the same agent induce amplified responses

Source: Curie Institute; Bryan, Garnier & Co ests.

How an effective immune response is mounted

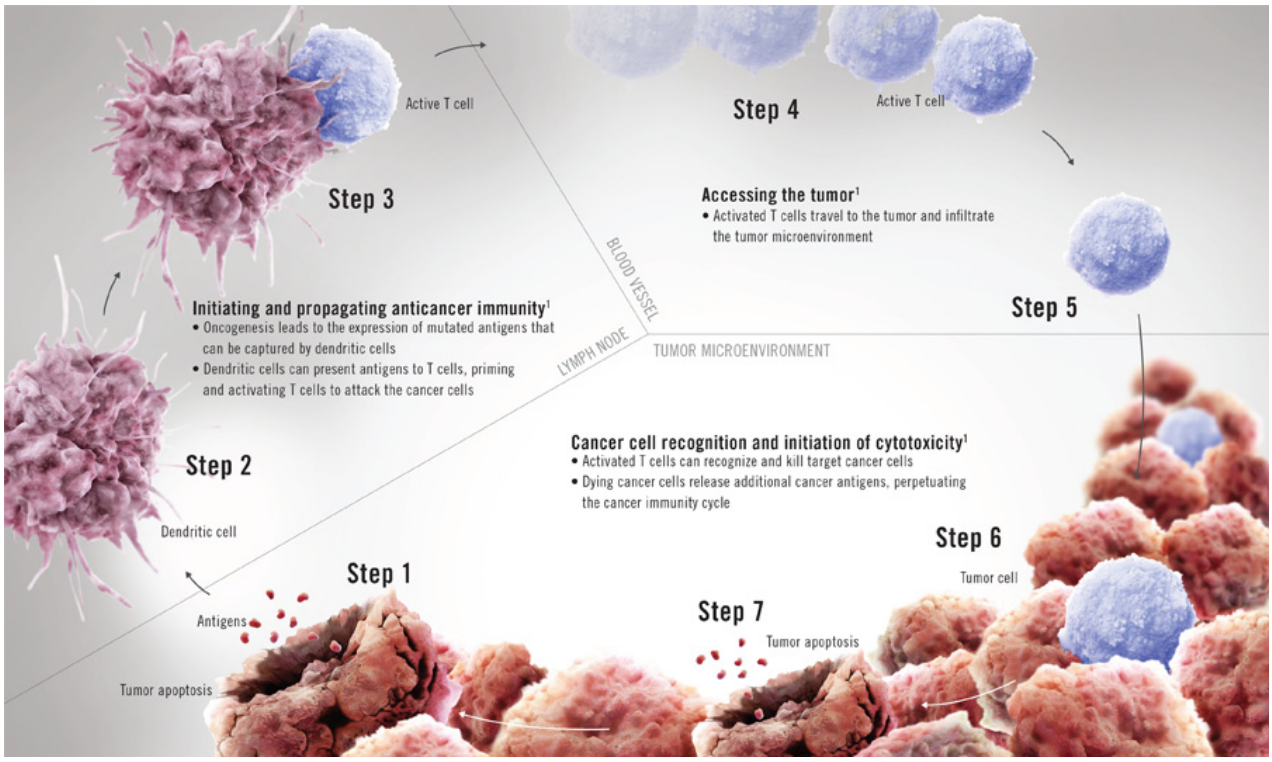
Now turning to the immune response against cancers, we can roughly divide it into three big steps ultimately leading to the death of cancer cells:

- **Initiating the anti-tumour response**. Neoantigens (i.e. antigens encoded by tumour-specific mutated genes) created by oncogenesis have to be recognised by innate cells before 1/ pro-inflammatory cytokines and factors are released to stimulate the overall system, and 2/ effector T lymphocytes (which by definition are the most potent of our immune soldiers) are activated by dendritic cells.

- **Trafficking to the tumour.** The activated effector T cells then migrate and infiltrate the tumour micro-environment (which is comprised of non-cancer cells and small proteins).

- **Recognising cancer cells and initiating cytotoxicity.** Once within the tumour bed, these immune cells specifically recognise/bind cancerous ones thanks to a specific receptor (known as TCR), and kill them… and, after that, more tumour-associated antigens are released, recognised, etc.

Fig. 3: The immune response cycle



Source: Research Cancer Immunotherapy; adapted from Chen et al.*, 2013.*

Many factors might explain the failure of an anti-cancer response… and the tumour micro-environment is a prominent one

On paper, such a cycle looks pretty well-rounded… but the reality is quite different, especially when it comes to cancer patients. The cancer-immunity cycle does not perform optimally due to a multiplicity of issues (non-detection of tumour antigens, generation of a Treg response following the recognition of the antigen as "self", loss of MHC expression, etc.)… which could be explained by numerous potential distorts in the cancer immuno-surveillance process leading to immune escape. Such a concept is currently known as **"the three Es of cancer immuno-editing"** and suggest that there are three phases of relation between cancer and our immune system: elimination, equilibrium and escape.

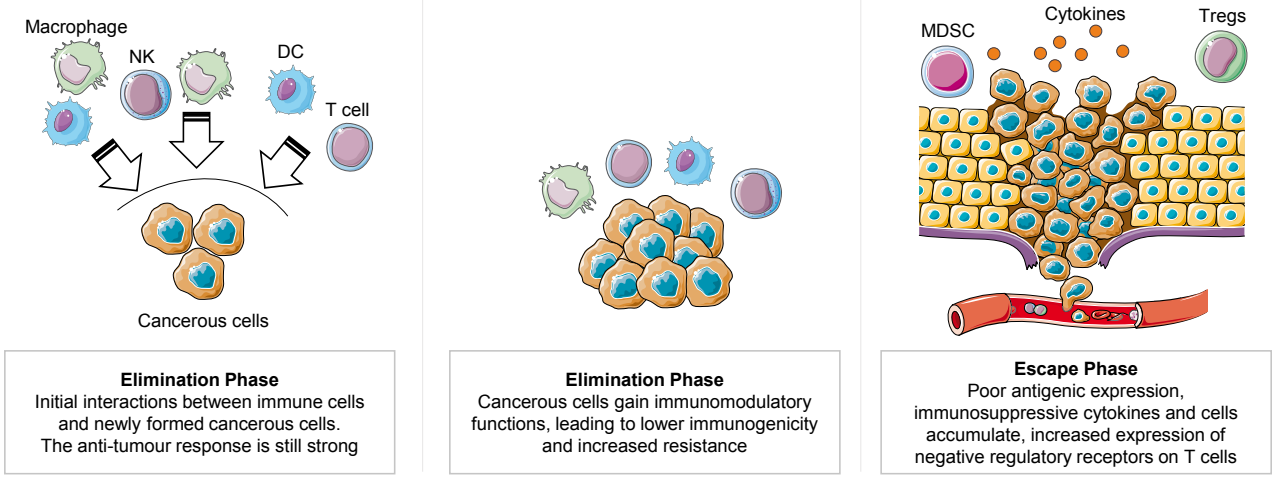
- **The three Es of cancer immuno-editing**

  - In the **Elimination** phase, malignant cells are quickly recognised and killed by immune cells for a wide range of reasons: antigens are significantly expressed and in a wide variety, few immune cells are "corrupted", etc.

  - In the **Equilibrium phase,** our immune system is still able to recognise cancer cells and continue to exert its pressure. But while many of the original variants are destroyed, new variants actually arise, and appear to be much more resistant to immune attacks.

  - **Escape**: tumour cell variants that have so far survived are completely resistant to immune detection and elimination thanks to a variety of mechanisms… and, in this case, the concept of tumour micro-environment appears to be key.

Fig. 4: From immuno-surveillance to immune escape (the three Es)

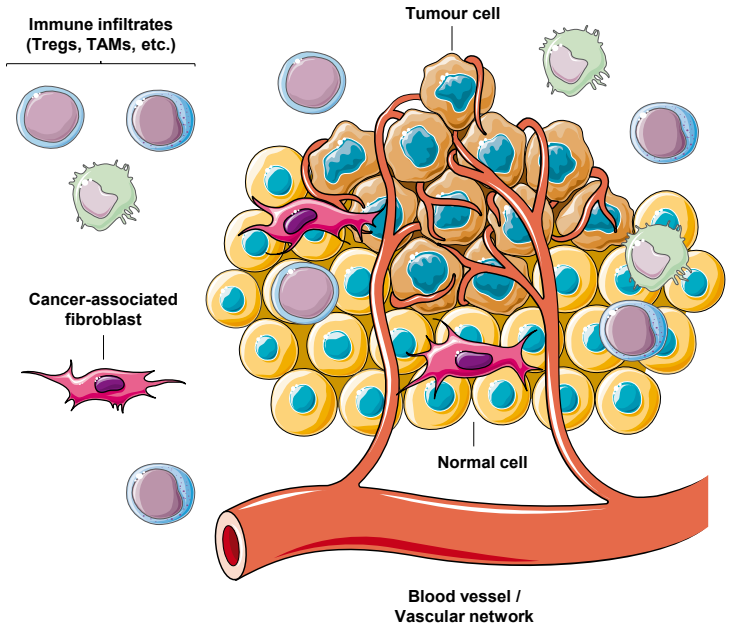


Source: Adapted from Kim et al., *2007; Bryan, Garnier & Co. ests.*

The tumour micro-environment: an increasingly key concept

The tumour micro-environment (TME) is a network of both malignant and non-malignant elements (immune cells, vasculature, cytokines and chemokines, etc.) forming an immuno-suppressive environment, which has caught significant momentum… and is now recognised as: 1/ **a key factor in multiple stages of the disease progression (e.g. local resistance, immune-escaping and metastasis)**; and 2/ an important "missing link" in our quest for more effective anti-cancer treatments.

Fig. 5: The TME: a quite complex ecology

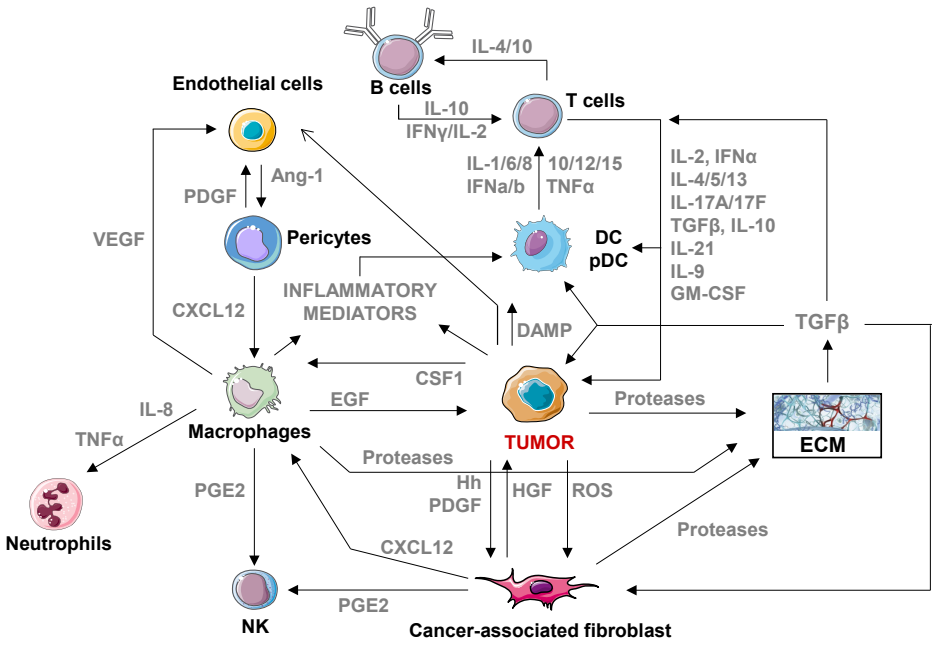


Source: Adapted from Nature; Bryan, Garnier & Co. ests.

Just to give an example, gliomas/brain tumours are known to: 1/ secrete immuno-suppressive factors such as TGF-β, IL-10 and CCL-2; 2/ recruit immune cells like regulatory T cells (Tregs) and myeloid-derived suppressive cells (MDSCs) to cancer cells, thus further developing a tumour-promoting milieu. In addition, these malignant cells express surface molecules such as Fas-ligand, B7-1/B7-2 and PD-L1/PD-L2 which, when bound to their respective receptors (Fas, CTLA-4 and PD-1) on tumour-infiltrating lymphocytes, alter and dampen their effector functions...

Some of these non-tumour/stromal cells – like Tregs – are already seen as promising therapy targets, especially in light of their genetic stability compared to the cancerous ones. But a delicate balance has to be found between inhibiting tumour-promoting activities and maintaining the normal functions of these cells…

Fig. 6: TME – Multiple activating and inhibitory intercellular signals



Source: Curie Institute; Bryan, Garnier & Co. ests.

3. From theory to practice: taylor-made strategies are key

Now let's turn to some more practical issues… In light of our discussions with Curie's specialists, here are our key messages for those investors willing to gain an increasing exposure to the immune-oncology field:

- **PD-1/PD-L1 inhibitors are likely to play a key role in the development of this nascent paradigm** given the impressive response rates and improvements in overall survival rates they have generated.

- **Monotherapies are not a panacea, and the best outcomes are likely to be achieved by combination therapies**; but :1/ obviously, not all of them will yield positive results; and 2/ each and every one of them are more susceptible to succeed in a given milieu/indication.

- **Understanding the mechanism of action of each compound, and thus their impact on the cancer-immune system interrelations (especially the TME), is key**… knowing that some pathways might be more important than others.

- Apart from a "simple" stratification of the patients depending on the characteristics of the tumour milieu, **we see molecules with potential predictive biomarkers as the ones with better probability of success**.

- Efficacy is of course of essence, but **one should not turn a blind eye to safety**.

3.1. PD-1/L1 inhibitors as strong backbones

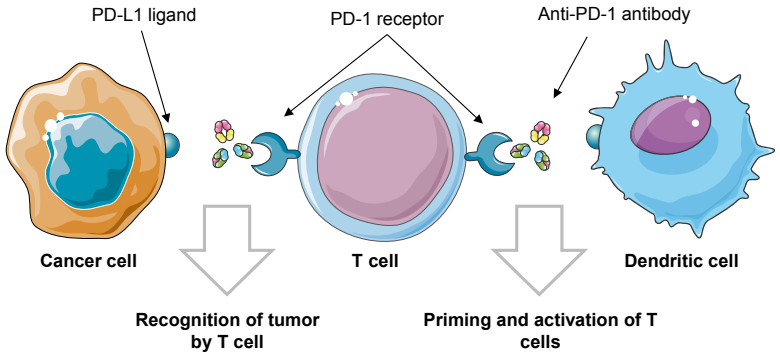
Checkpoint inhibitors, and particularly anti-PD-1/PD-L1s, are likely to be part of the future SOC

For quite a long time, the scientific community has been rather sceptical when it comes to immune-oncology (I-O) agents… certainly because of a lack of understanding, along with the use of non-specific approaches (e.g. IL-2, TNF-α). But, notably since the regulatory approval of ipilimumab (an anti-CTLA-4 mAb), the field has been experiencing a complete renaissance… and particularly in immune checkpoint inhibitors.

Before going into further details, **let's define what the so-called "immune checkpoints" are**, and why their blockade is such an interesting therapeutic strategy. To put it as simply as possible, our immune system is full of police roadblocks: each cell is controlled by our immune soldiers and has to present some surface proteins that act as ID cards. And if such a protein suggests that the cell is infected/dangerous, an immune attack is unleashed… leading to the cell's death. That said, cancer cells are foxy, and sometimes act as normal ones to survive, by presenting false ID cards. Hence, the aim to prevent this through some specific immune checkpoint blockers/inhibitors.

Immune checkpoint blockers are currently among the most promising anti-cancer approaches. CTLA-4 was the very first target that significantly improved overall survival in patients with a quite challenging tumour type (metastatic melanoma), and led to the approval of the very first compound within this novel therapeutic class (BMS's Yervoy, also known as ipilimumab). But even better outcomes have now been reached with anti-PD-1/PD-L1 in a range of different indications, and especially in patients overexpressing the ligand PD-L1 (but we'll come back later to this particular topic)…

Fig. 7: Mechanism of action for a checkpoint inhibitor targeting PD-1



Source: Bryan, Garnier & Co. ests.

Fig. 8: Anti-PD-1/PD-L1 – Overall response rates (%)

Indication	Response rate (%)
Non-small cell lung cancer (NSCLC), squamous and non-squamous	15-20%
Small cell lung cancer (SCLC)	15%
Renal cell Carcinoma (RCC)	15-20%
Bladder cancer	25%
Head & neck squamous cell carcinoma (HNSCC)	15-25%
Gastric cancer	20%
Hepatocellular carcinoma (HCC)	20%
Hodgkin's Lymphoma (HL)	65-85%
Ovarian cancer	15%
Triple negative breast cancer (TNBC)	20%

Source: Curie Institute; Bryan, Garnier & Co.ests.

That said, these blockers are far from perfect as the overall response rates vary between 15% and 30% should we limit ourselves to solid tumours. And: 1/ these quite low levels can certainly be explained by the fact that these approaches solely target one immune axis; and 2/ such heterogeneity is also attributable to the inter-tumour heterogeneity and the complexity of the tumour micro-environment. Add to this a growing understanding of the numerous immune-tumour interactions, it was only natural for the industry and scientific community to test different novel combination regimens…

3.2. Combining to better address a tumour's heterogeneity and complexity

Going from the tumour specifics to choosing the right combination

In essence, here are the following points we would keep in mind following the presentations and discussions with Curie's specialists (at least when it comes to combinations):

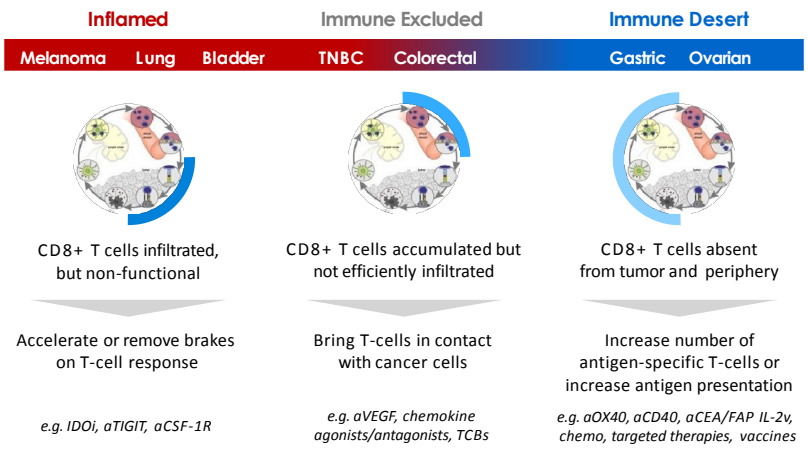
- **The optimal anti-tumour response will require the successful modulation of several pathways/fronts**. There is no "one-fits-all" strategy (and that's why some approaches long failed as a monotherapy, e.g. cancer vaccines); and the best outcomes will probably be achieved by attacking multiple fronts in a targeted manner.

- **Evaluating the cancer micro-environment will be key to gauging/selecting the best agents to be used;** all the more so as: 1/ the efficacy profile of a given agent can be significantly impacted by the TME (e.g. checkpoint blockers are less likely to generate responses in lowly inflamed tumours); 2/ simply adding a compound to another is clearly not the right strategy; and 3/ analysing the tumours will be key to know which immuno-suppressive pathway is hampering the cocktail's effects.

- **Compounds targeting a unique factor within the TME might fail, notably because such factor plays a petty role**… and unfortunately giving an estimation of its relative importance is no easy task (many immunologists and companies, for instance, thought that the PD-1/PD-L1 axis was a minor one).

- Lately, Roche has been stratifying patient populations depending on: 1/ the level of infiltration of CD8+ T lymphocytes, along with their presence in the periphery; 2/ how immunogenic the tumour is; and 3/ the expression of PD-L1. Based upon this nomenclature, the big pharma industry currently thinks that nearly 60-70% of cancers could be considered as an "immune desert" (lowly immunogenic, no T cell infiltration, exhausted immune cells).

Fig. 9: Stratification of patients depending on tumour specifics

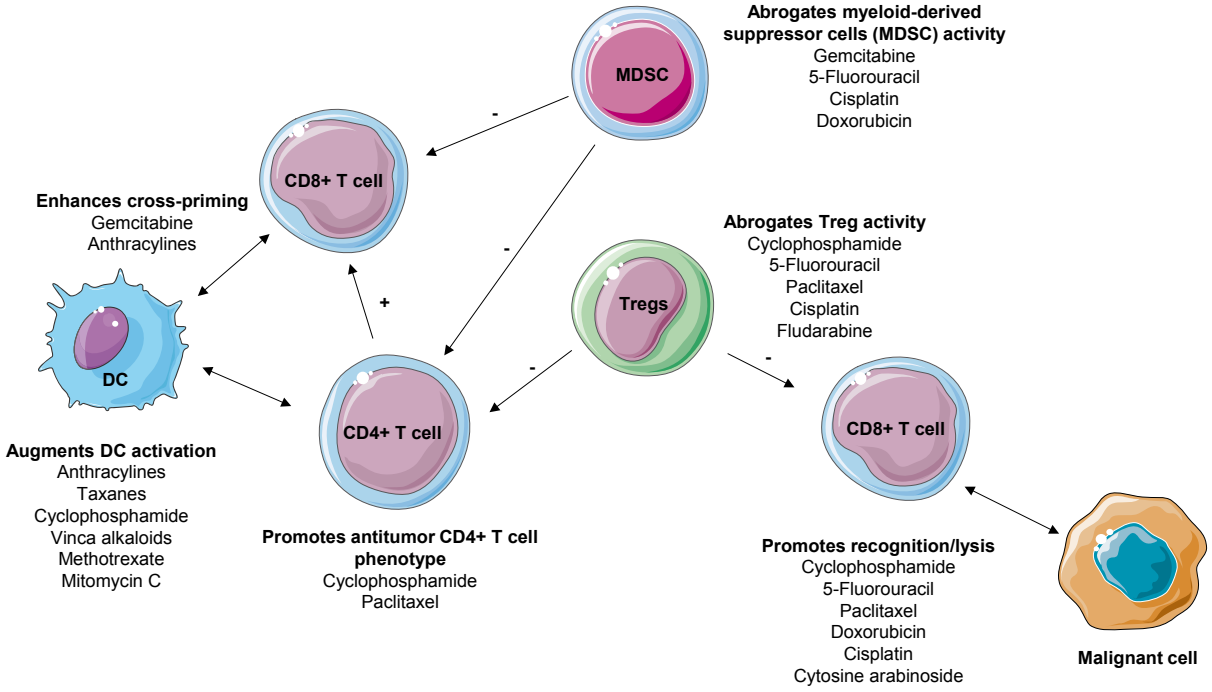


Source: Roche, BG Oncology Day (2016)

- **More "traditional" therapies (e.g. chemo, radiation, etc.) will play a key role in the future paradigm**, be it because: 1/ some of them are much more affordable than their more innovative counterparts… or 2/ their mechanism of action is pretty synergistic with I-O agents. Chemotherapies are immune suppressive and thus were long considered as contra-productive in the current paradigm. It is now widely accepted that some of these can actually augment tumour immunity; be it: 1/ by inducing immunogenic cell death and leading to the release of cancer antigens ("debulking"), or 2/ by disrupting strategies that cancer cells use to evade immune suppression (including the abrogation of immuno-suppressive cells within the TME, such as Tregs).

- **Targeted therapies (e.g. anti-ALK, anti-EGFR) are also believed to afford a favourable window for immunotherapy to achieve more cytotoxicity** due to: 1/ their ability to rapidly induce pretty deep responses, and 2/ their potential impact on the TME (reduced immuno-suppression, unleashing of neoantigens, etc.). That said, these approaches are likely to be considered solely if the genetic profile of the patient corresponds with the afferent classification.

Fig. 10: How chemotherapies modulate tumour immunity



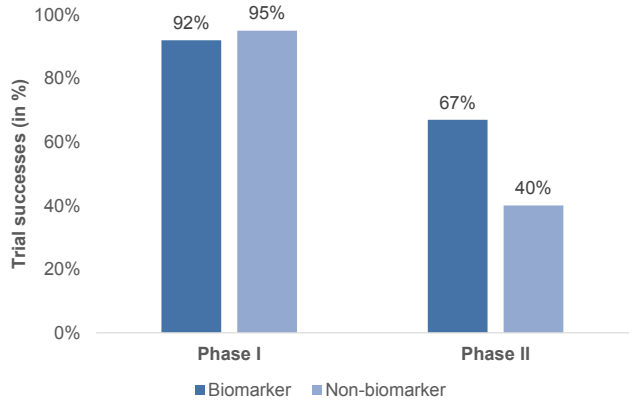
Source: Adapted from Emens et al. *2015, Bryan, Garnier & Co. ests.*

3.3. The quest for biomarkers continues

Predictive biomarkers as must-haves

The quest for biomarkers dates back to the development of the first targeted therapies directed at tumours with specific mutation types. Today, the development of a drug is often associated with the hunt for a predictive biomarker which helps to stratify patients better and maximise the success of clinical trials. I-O is no exception to the rule, and **biomarkers are believed to become must-haves in the development of oncology treatments going forward**.

Fig. 11: NSCLC trial success for molecules with and without biomarkers



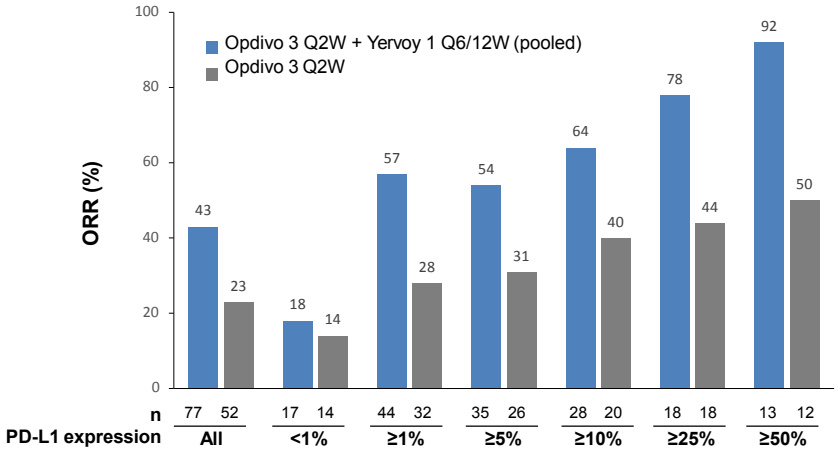
Source: Journal of Thoracic Oncology, 2014; 9 (2): 163.

PD-L1 expression as a primary basis for stratification

Responses to PD-1/PD-L1 blockers are positively correlated to the expression of PD-L1…

The initial data collected by BMS, Merck & Co., Roche and AstraZeneca look fairly unanimous: the response along with its duration tend to be much more significant when patients over-express the PD-L1 ligand (be it solid tumours or haematological malignancies)And that's why some of these companies have decided to use this first element of stratification as a key cornerstone in designing their trials.

Fig. 12: NSCLC trial success for molecules with and without biomarkers



Source: BMS

Fig. 13: PD-L1 expression depending on the type of tumour

Cancer type	PD-L1 expression	Tumour-infiltrated immune cells?
Melanoma	40-100%	Yes
Non-small cell lung cancer	35-95%	Yes
Nasopharyngeal	68-100%	Yes
Glioblastoma	100%	Yes
Colon adenocarcinoma	53%	Yes
Hepatocellular carcinoma	45-93%	Yes
Urothelial/bladder	28-100%	Yes
Multiple myeloma	93%	Yes
Ovarian	33-80%	Yes
Gastric carcinoma	42%	Yes
Oesophageal	42%	Yes
Pancreatic	39%	Yes
Renal cell carcinoma	15-24%	Yes
Breast	31-34%	Yes
Lymphomas	17-94%	Yes
Leukaemias	11-42%	No

Source: Research Cancer Immunotherapy; Bryan, Garnier & Co. ests.

… But such a basis for stratification is far from perfect

However, **simply retaining the PD-L1 status might not be the right strategy** as: 1/ its expression can apparently vary over time, and even within different regions of the same tumour, under the influence of different factors (e.g. IFN-γ); 2/ as previously underlined, PD-1/PD-L1 is just one immune checkpoint among others; and 3/ patients diagnosed in late stages of a cancer (III-IV) might have inaccessible tissues or a sample that cannot be evaluated; e.g. in advanced or metastatic NSCLC, 31% of patients have inaccessible tissue and 25% of sample tissues cannot be processed because of their heterogeneity, improper conservation or instability.

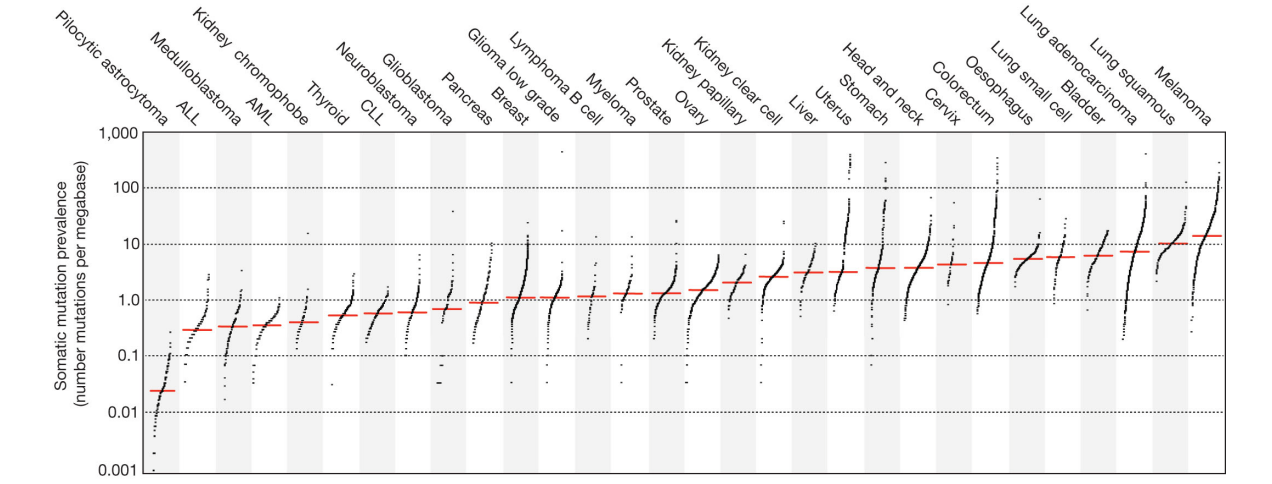
Note that a liquid biopsy might be a first answer to the latter issue and, particularly, the analysis of cell free DNA currently investigated in clinical trials. This approach focuses on the analysis of cell free nucleic acids which are thought to originate from dead cells and which have been shown to contain cancer-related mutations. However, the variation of concentration in the bloodstream raises challenges with regard to the enrichment of the sample and the sensitivity of the test.

- **Other potential markers are currently under investigation**

Other promising markers are under investigation

The use of MMR deficiency (DNA mismatch repair) as a potential predictive marker for checkpoint blockers, for example, has gained traction immensely over the past few months; particularly following the publication of an ORR of 62% in heavily pre-treated patients with metastatic colorectal cancer exhibiting such a deficiency (5-10% of them). That said, other alternatives are needed for the remaining 90-95%... And that's why Merck & Co is investigating a wide range of other possibilities (e.g. the IFN-γ signature).

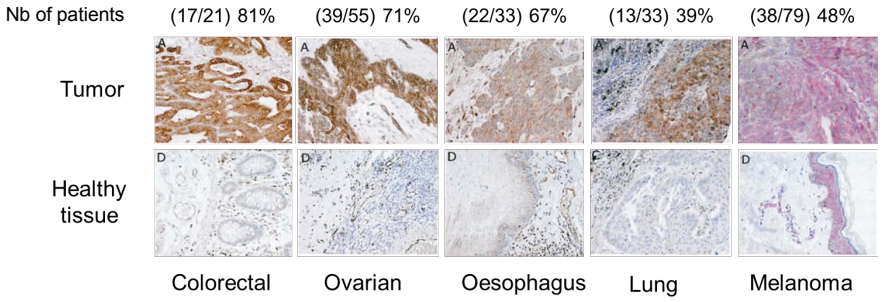
Fig. 14: Mutation frequencies in protein-coding regions



Source: LB Alexandrov et al.*, Nature (2013)*

Among others, **Innate Pharma and AstraZeneca's biomarker strategy for monalizumab (anti-NKG2A) looks pretty attractive in our view**. HLA-E, which is NKG2A's ligand, might indeed be a much more reliable predictive biomarker than PD-L1 as: 1/ this protein is known to be overexpressed in many tumour types (see Fig. 15), in a quite stable manner; 2/ its expression on healthy tissues is said to be fairly restricted; and 3/ research studies suggest that its overexpression could be an important poor prognosis factor, especially in ovarian cancer (Gooden *et al.*, 2012).

Fig. 15: HLA-E expression depending on the tumour type



Source: Innate Pharma

3.1. And don't forget the safety belt!

One should not turn a blind eye to safety

One of the speakers made a particular focus on the importance of anticipating and managing immune-related adverse events, all the more so as: 1/ oncologists practicing in small clinics are probably not yet accustomed to such toxicity profiles; and 2/ such risks are exacerbated with combinations. As an example, nivo/ipi did significantly improve response rates vs either nivo or ipi as single-agents… But at the expense of a nearly exponential increase in Grade 3-4 adverse events (55% vs 16% and 27% respectively); and ultimately more discontinuations.

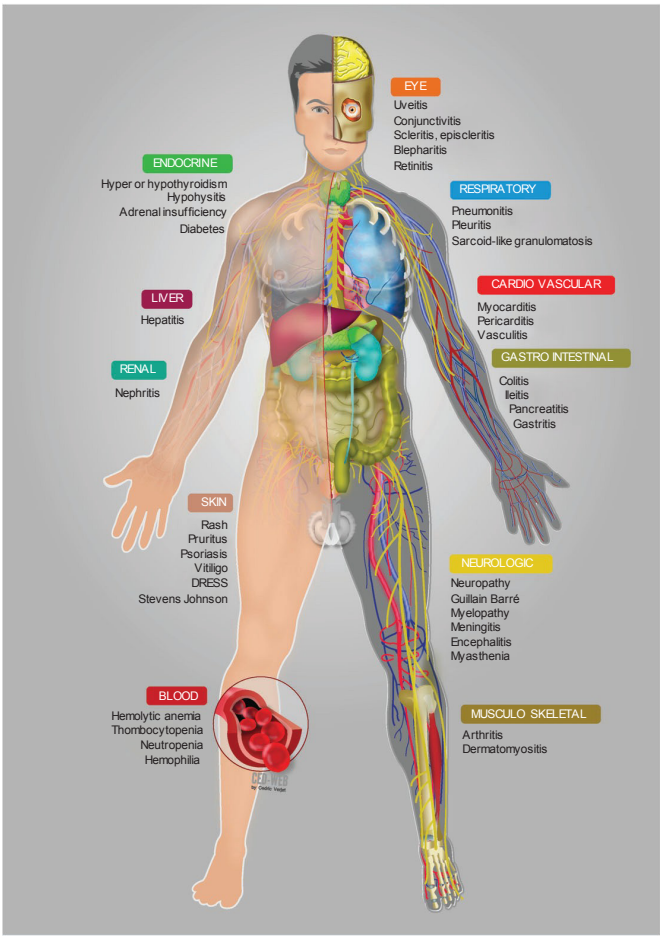
Obviously, a balance has to be found to minimise toxicity while preserving efficacy… Be it through changes in administration sequences (Weber *et al.*, 2016) or the combination with other compounds.

Fig. 16: Nivo/ipi in untreated melanoma – Adverse events

Event	Nivolumab		Ipilimumab		Nivo/Ipi	
	Any	Grade 3-4	Any	Grade 3-4	Any	Grade 3-4
Treatment-related adverse events	**82%**	**16%**	**96%**	**55%**	**86%**	**27%**
Diarrhea	19%	2%	44%	9%	33%	6%
Fatigue	34%	1%	35%	4%	28%	1%
Pruritus	19%	0%	33%	2%	35%	0%
Rash	26%	1%	40%	5%	33%	2%
Nausea	13%	0%	26%	2%	16%	1%
Pyrexia	5%	0%	19%	1%	7%	0%
Decreased appetite	11%	0%	18%	1%	13%	0%
Increase in alanine amino-transferase level	4%	1%	18%	8%	4%	2%
Vomiting	6%	0%	15%	3%	7%	0%
Increase in aspartate amino-transferase level	4%	1%	15%	6%	4%	1%
Hypothyroidism	9%	0%	15%	0%	4%	0%
Colitis	1%	1%	12%	8%	12%	9%
Treatment-related AE leading to discontinuation	**8%**	**5%**	**36%**	**29%**	**15%**	**13%**

Source: NJEM; Bryan, Garnier & Co ests.

Fig. 17: Spectrum of toxicity of immune checkpoint blockade agents



Source: Champiat et al.*, 2015*

4. Five names to play the field in 2016 and 2017

From a stock market perspective, **we have identified five companies within our coverage with strong cancer-related catalysts over the next few months: Roche, AstraZeneca, Genmab, Ipsen and Innate Pharma.**

Fig. 18: BG coverage – Companies with the strongest cancer-related catalysts

Company	Compound(s)	Indication	Stage	Catalyst
AstraZeneca	Acalabrutinib	Relapse CLL	Phase III	Data readout in H2 16
	Durvalumab	R/R Head & neck cancer	Phase II	Data readout in H2 16
	Durvalumab + Tremelimumab	1L Non-small cell lung cancer	Phase III	Data readout in H1 17
	Lynparza (olaparib)	BRCA+ Ovarian cancer	Phase III	Data readout in H2 16
Roche	Perjeta (pertuzumab) + SOC	Adjuvant HER2+ breast cancer	Phase III	Data readout in H2 16
	Gazyva (obinutuzumab)	CD20+ Diffuse large B cell lymphoma	Phase III	Data readout in H2 16
	Tecentriq (atezolizumab)	2/3L Non-small cell lung cancer	Phase III	Data readout in H2 16
Ipsen	Cometriq (cabozantinib)	2L Renal cell carcinoma	MAA	Approval in H2 16
	Cometriq (cabozantinib)	1L Renal cell carcinoma	Phase II	Data readout in H2 16
Genmab	Darzalex (daratumumab)	2/3L Multiple myeloma	MAA	Label expansion in Q4 16
	Darzalex (daratumumab)	2/3L Multiple myeloma	MAA	POLLUX follow-up (ASH?)
	Darzalex (daratumumab)	R/R Non-Hodgkin Lymphomas	Phase II	Data readout in Q4 16 (ASH?)
Innate Pharma	Lirilumab	Acute myeloid leukaemia (maintenance)	Phase II	Data readout in H2 16
	Lirilumab + Opdivo (nivolumab)	Solid tumours	Phase Ib	Data readout in Q4 16 (ESMO?)
	Monalizumab	Solid tumours	Phase II	Data readout in 2017

Source: Company Data; Bryan, Garnier & Co ests.

4.1. AstraZeneca: acalabrutinib will drive the franchise in H2 16

4.1.1. Acalabrutinib to become a major candidate for AZN

An increasing interest in BTK inhibitors following ibrutinib's outstanding results in CLL

BTK inhibitors have particularly been under the spotlight following JNJ/AbbVie's unprecedented clinical results in different haematological malignancies, and notably in Chronic Lymphocytic Leukaemia or CLL…The most obvious example stems from the phase III RESONATE study involving refractory or relapse patients for more than one therapy, and ofatumumab (anti-CD20) as a comparator (ORR: 90% vs 25%, 90% reduction in risk of progression or death after 16 months of follow-up). As proof of the rising interest in this therapeutic class, AZN acquired Acerta a few months ago to get its hands on **acalabrutinib, a second-generation inhibitor… for which some phase III data vs ibrutinib in CLL are expected by the end of this year.**

We are taking the opportunity of this feedback note to integrate this potential blockbuster in our model (impact on our FV: +GBp400, although partially offset by downgrades, including on ZS-9).

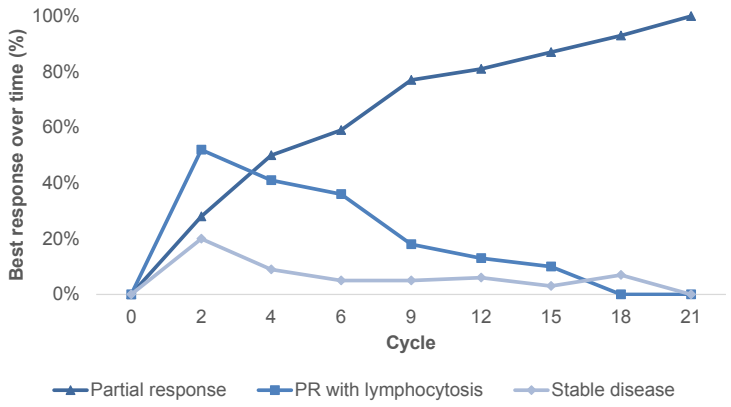
■ **Acalabrutinib: the best BTKi-in-class in CLL**

AZN's acalabrutinib might be a more potent and yet safer option than ibrutinib

It is currently assumed that "acala" could display an improved risk-benefit profile as a treatment for this particular disease thanks to its greater selectivity for BTK… Because targeting this enzyme in a more selective and sustained manner might: 1/ reduce the potential toxic side-effects associated with the inhibition of several other kinases (e.g. EGFR, TEC, ITK, etc.); and 2/ allow longer durations of treatment (which is essential to maintain/deepen the responses.

In this regard, the phase Ib data in relapse CLL tended to confirm such assertions as: 1/ they showed that the observed responses deepened over time irrespectively of the chromosomal status, in patients who received a median of three prior lines; 2/ at 12 months, such an indicator stood at nearly 80% (vs 43% for ibrutinib in the RESONATE study).

Fig. 19: Phase I results for acalabrutinib in CLL (R/R)



Source: AstraZeneca, Acerta Pharma acquisition (Dec 2015)

Safety-wise, the side-effects tend to be far less severe and numerous than with ibrutinib (see Fig. 20). Among others, we would note that: 1/ Grade 3-4 neutropenia, pneumonia and thrombocytopenia were not heralded as common AEs (vs 16%, 7% and 6%); and 2/ not a single-case of Richter's transformation was observed after a median follow-up of more than a year.

Be it from an efficacy or financial perspective, this will be far from insignificant as: (i) many fewer patients would discontinue their treatment due to an unfavourable safety profile (in other words, an increasing number of them would be treated for a longer period of time); and (ii) this makes it a less challenging candidate to be combined with.

Fig. 20: Safety profile of acalabrutinib in relapsing CLL (n=61)

Adverse event	All grades	Grades 1-2	Grades 3-4
Headache	43%	43%	0%
Diarrhea	39%	38%	2%
Increased weight	26%	25%	2%
Pyrexia	23%	20%	3%
Upper respiratory tract infection	23%	23%	0%
Fatigue	21	18%	3%
Peripheral edema	21%	21%	0%
Hypertension	20%	13%	7%
Nausea	20%	20%	0%
Confusion	18%	18%	0%
Arthralgia	16%	15%	2%
Petechiae	16%	16%	0%
Decreased weight	16%	16%	0%

Source: Company Data; Bryan, Garnier & Co ests.

- **We anticipate a non-risk-adjusted peak sales of USD2.5bn in CLL**

Estimated peak sales of USD2.5bn in CLL in 2024

We believe acalabrutinib will be major compound for AstraZeneca, as we forecast peak sales in CLL of USD2.5bn in 2024. Given the pretty deep and durable responses that acalabrutinib was able to induce as a monotherapy in CLL, we assume: 1/ it could grab nearly 20% of this market; and 2/ its cost per patient would be similar to ibrutinib's.

Fig. 21: AZN – Acalabrutinib – Sales estimates

	USA	Europe	TOTAL
First-line patients			
Incidence (2016)	15,655	16,160	31,815
Annual cost of treatment (USD)	100,000	75,000	
Duration of treatment (in years)	3	3	3
Market shares at peak (%)	20.0%	20.0%	
Peak year	2023	2024	2024
Peak sales (EURbn) - Non-risk-adjusted	**1.0**	**0.8**	**1.8**
Second-line patients			
Incidence (2016)	15,655	16,160	31,815
Annual cost of treatment (USD)	100,000	75,000	
Duration of treatment (in years)	2	2	2
Market shares at peak (%)	20%	20%	
Peak year	2021	2022	2022
Peak sales (EURbn) - Non-risk-adjusted	**0.4**	**0.3**	**0.8**

Source: Bryan, Garnier & Co ests.

Obviously, **CLL is not the sole market that AZN intends to address**, all the more so as the disruption of this particular part of the BCR signalling pathway previously proved to be quite efficient in different Non-Hodgkin's Lymphomas (mantle cell lymphoma, follicular lymphoma and non-ABC diffuse large B cell lymphoma)… **But we have decided to retain a considerably lower PoS for these indications pending the publication of further clinical data**.

■ **What about the synergies with I-O agents?**

But "acala" might have less synergies with I-O agents

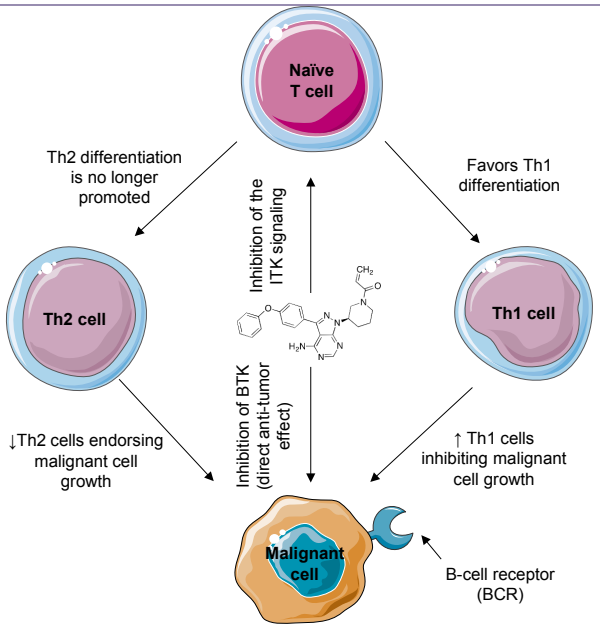
Acalabrutinib undoubtedly is a very promising candidate within AZN's portfolio and we believe the Street will increasingly see it as a major driver of its oncology franchise. That said, we have to admit that not inhibiting ITK might limit the modulation of the Th1/Th2 immune response. This is not to say that "acala" would be a less attractive partner for combination with I-O agents. But we believe this might reduce its chances of success in solid tumours (in which ibrutinib is trying to make a breach).

Fig. 22: Acalabrutinib – Kinase inhibitions

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	93	7
BMX	46	0.8
TXK	368	2
ERBB2	around 1,000	6.4
EGFR	> 1,000	5.3
ITK	> 1,000	4.9
JAK3	> 1,000	32
BLK	> 1,000	0.1

Source: Byrd et al. *(2016); Bryan, Garnier & Co. ests.*

Fig. 23: Ibrutinib – Immunomodulatory properties



Source: Ansell et al.; *Bryan, Garnier & Co. ests.*

4.1.2. Durvalumab: confirmation needed

- **As a single-agent in 2L head & neck cancer**

Metastatic head and neck cancer is one of the few indications in which PD-1/PD-L1 inhibitors have already showed some pretty interesting responses as single-agents; and we note that durvalumab managed to yield an ORR of 18% in PD-L1+ relapse/refractory patients (vs 8% of negative ones). In essence, these data compared more than favourably with the anti-EGFR cetuximab (10%); but also appeared less impressive than Merck & Co's pembrolizumab (ORR: 25% with most of those patients being PD-L1 over-expressors).

Against this backdrop, we would deem as positive an ORR in the range of 20-30% (knowing that the trial exclusively enrolled PD-L1+ patients)… Bearing in mind that AZN's "durva" might differentiate itself in the long run with some unique combinations, and particularly the one with Innate Pharma's monalizumab (an anti-NKG2A).

Fig. 24: Pembrolizumab efficacy results in recurrent and/or metastatic HNSCC

Best overall response	Total (n=117)	HPV+ (n=34)	HPV- (n=80)
ORR	29 (24.8%)	7 (20.6%)	21 (26.3%)
Complete response	1 (0.9%)	1 (2.9%)	0 (0%)
Partial response	28 (23.9%)	6 (17.6%)	21 (26.3%)

Source: Merck & Co, ASCO 2015 presentation

- **… And with tremelimumab in 2L head & neck cancer**

Here again, the question is not so much whether durvalumab/tremelimumab might outmatch "durva" alone as previous results showed a tremendous improvement in both PFS and OS; but rather if such a cocktail does compare favourably with BMS's nivolumab/ipilimumab in both the efficacy (see Fig. 25) and the safety side.

Fig. 25: Nivolumab/Ipilimumab in 1L NSCLC – Efficacy profile

	Opdivo 3 Q2W + Yervoy 1 Q12W	Opdivo 3 Q2W + Yervoy 1 Q6W	Opdivo 3 Q2W
ORR (%)			
< 1% PD-L1	30%	0%	14%
≥ 1% PD-L1	57%	57%	28%
≥ 50% PD-L1	100%	86%	50%
Median PFS, in months			
< 1% PD-L1	4.7	2.4	6.6
≥ 1% PD-L1	8.1	10.6	3.5
≥ 50% PD-L1	13.6	Not reached	8.4
1-year OS rate (%)			
< 1% PD-L1	Not calculated	Not calculated	79%
≥ 1% PD-L1	90%	83%	69%
≥ 50% PD-L1	Not calculated	100%	83%
Median follow-up, in months	**12.9**	**11.8**	**14.3**

Source: BMS; Bryan, Garnier & Co ests.

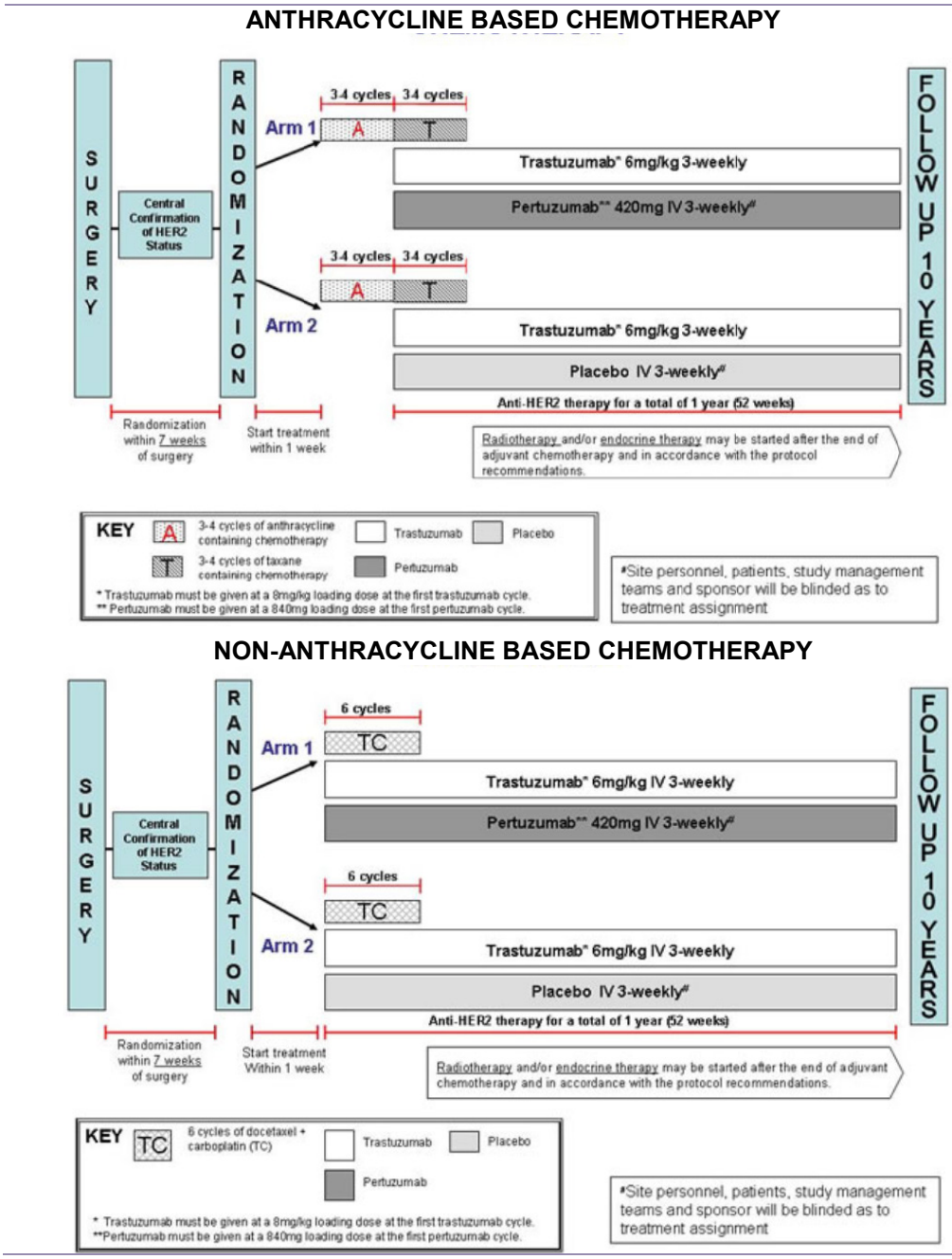
4.2. Roche: all eyes on APHINITY

- **APHINITY: a game-changing catalyst**

At least three cancer-related clinical publications are likely to drive ROG shares in the next few months; but obviously, we deem APHINITY will be the most game-changing one as, depending on the outcome, the company's growth profile would be profoundly modified by the end of the decade.

APHINITY is a phase III study evaluating Perjeta (pertuzumab) in combo with Herceptin (trastuzumab) and chemotherapy in adjuvant HER2+ primary breast cancer, knowing that the primary endpoint is disease-free survival or DFS.

Fig. 26: APHINITY – Trial design



Source: IBCSG

"In terms of design, we think we've done everything well" said Roche representatives at our meeting, adding that "a fail would be a surprise", reporting more than a 50% chance of success. The rationale for combining Herceptin and Perjeta is now set and, although adjuvant BC is a different setting with minimal residual disease and if the population recruited differs by some aspects (less node-negative tumours), it should work equally well.

- **Two other catalysts: GOYA and "atezo" vs chemo in 2L NSCLC**

GOYA is a phase III study that is investigating Gazyva (obinutuzumab) vs Rituxan (rituximab) on top of the CHOP CT regimen in patients with CD-20 positive diffuse large B-cell lymphoma, usually referred to as aggressive NHL. The study is expected to report results by year-end in about 1,400 patients with the primary endpoint being PFS. Although Gazyva proved superior in CLL and in indolent NHL (GALLIUM), Roche considers that the history of the drug in this disease is such that the risk of failure is largely carried from phase I/II into phase III because only ORR has been clearly assessed so far. This is largely a different disease where an anti-CD20 drug is expected to extend life in iNHL, whereas it can be curative in DLBCL. If GOYA is positive, this would be very good news one-year ahead of biosimilar rituximab's expected launch in first markets, considering also the premium price for Gazyva.

Somewhat less significant for Roche, but meaningful anyway as it relates to atezolizumab, are the phase III results from the OAK trial which is assessing the benefit of the anti-PD-L1 in monotherapy in second-line NSCLC vs docetaxel in more than 1,200 patients. The primary endpoint is OS which obviously gives this drug a great chance of success in the trial but the results will of course be compared with those already reported with Keytruda and Opdivo in similar settings. Although Roche does not make monotherapy a big deal with "atezo", it will be interesting to see if its compound is at least as potent as competitors in a similar setting whatever next developments say. To note is that several other phase III data should be reported with atezo in lung, renal and bladder cancers next year.

4.3. Innate Pharma: strong newsflow ahead!

Phase Ib data involving lirilumab (anti-KIR) in combination with nivolumab (anti-PD-1) are to be presented either at the annual ESMO congress (October, 7-11) or the SITC (November, 9-13); and we believe they **will notably involve relapsing/refractory patients with solid tumours rather** than liquid ones, as the involved trial started quite a long time ago (2012).

- We reiterate our positive opinion on this combo regimen in light of all the synergies between NK-cell and T-cell approaches / the innate and the adaptive immune parts (see our initiation report for further details).

- In our view, **the best responses are likely to be achieved in more or less "inflamed" / immunogenic tumours** like melanoma, lung, and head & neck; and especially those for which paclitaxel and cisplatin were widely used as previous treatments (see Fig. 15 for further details on their immunomodulatory properties). And, in contrast, we're much more cautious when it comes to gastrointestinal cancers (GI) and hepatocellular carcinomas (HCC).

- **We'll pay particular attention to potential *post-hoc* analyses which would take into account the characteristics of the TME**. Just as an example, tumours with high levels of proangiogenic factors (e.g. VEGF) are a source of an abnormal vasculature that is particularly resistant to the influx of effector cells… And, as such, lower responses could be expected in such a setting.

- Overall, **we believe the combo will display a very satisfying safety profile**, particularly when compared to the nivo/ipi regimen (liri having solely displayed 19% of treatment-related Grade 3-4 adverse events irrespectively of the dose)… And, as previously underlined, such a characteristic is far from insignificant.

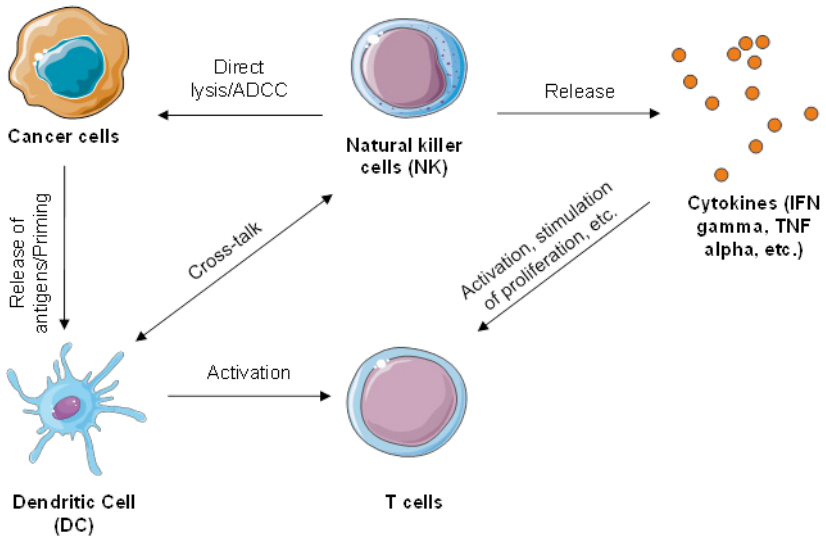
- Unfortunately, the trial remains a single-arm one… But we can say the ORR threshold to attain in R/R patients with melanoma or NSCLC is between 30% and 50% (which is more or less what we saw with the PD-1/CTLA-4 cocktails) irrespective of the PD-L1 expression.

Fig. 27: Response rate of combinations in solid tumours (all comers)

Candidate 1	Candidate 2	Indication	ORR all comers
Pembrolizumab (anti-PD-1)	Epacadostat (IDOi)	Immunotherapy-naïve melanoma	53%
Pembrolizumab (anti-PD-1)	Epacadostat (IDOi)	Immunotherapy-naïve NSCLC	38%
Pembrolizumab (anti-PD-1)	Epacadostat (IDOi)	Immunotherapy-naïve RCC	25%
Pembrolizumab (anti-PD-1)	Ipilimumab (anti-CTLA-4)	2/3L NSCLC	33-50%
Pembrolizumab (anti-PD-1)	Pemetrexed + Carboplatin	1L NSCLC	58%
Nivolumab (anti-PD-1)	Ipilimumab (anti-CTLA-4)	1L NSCLC	13-39%
Nivolumab (anti-PD-1)	Paclitaxel + Carboplatin	1L NSCLC	47%
Nivolumab (anti-PD-1)	Ipilimumab (anti-CTLA-4)	1L Melanoma	58%
Nivolumab (anti-PD-1)	Ipilimumab (anti-CTLA-4)	1L RCC	38-40%
Atezolizumab (anti-PD-L1)	Vemurafenib (BRAFi)	1L BRAF+ Melanoma	76%
Atezolizumab (anti-PD-L1)	Bevacizumab (anti-VEGFR)	1L RCC	40%
Atezolizumab (anti-PD-L1)	Nab-paclitaxel	1L TNBC	67%
Atezolizumab (anti-PD-L1)	Nab-paclitaxel	2/3L TNBC	25-29%
Durvalumab (anti-PD-L1)	Tremelimumab (anti-CTLA-4)	Immunotherapy-naïve NSCLC	27%
Ipilimumab (anti-CTLA-4)	Talimogene laherparepvec (virus)	1L Melanoma	50%

Source: Companies Data; Bryan, Garnier & Co ests.

Fig. 28: Direct and indirect anti-tumour action of natural killer cells (NK)



Source: Bryan, Garnier & Co ests.

4.4. Genmab: Q4 16 to seal the outperformance deal

■ **Many positive catalysts expected by the end of the year**

Genmab is already outperforming its peers thanks to the stellar data generated by daratumumab (an anti-CD38) in multiple myeloma as part of a combination regimen (and particularly with Celgene's Revlimid or lenalidomide)… And we believe that Q4 16 should lead to further progress as:

- **We assume the FDA will grant a priority review to "dara", as a treatment for patients with myeloma who received at least one prior therapy, in July or August** (which would pave the way for a label expansion by the end of the year… and thus another increase to our FV).

- **Phase II results involving "dara" in Non-Hodgkin's Lymphomas are expected in Q4 16**, and we currently view this catalyst as a free call option potentially offering further significant upside as: 1/ the consensus sees little value in these developments; and 2/ the underlying market is far from insignificant (around USD5bn by 2020).

- **Genmab and JNJ are likely to present some follow-up data from the POLLUX and CASTOR trials during the 2016 ASH meeting**… And we believe they will point to further improved hazard ratios for PFS (progression-free survival).

- We assume the very first phase III data (ALCYONE) involving daratumumab in newly-diagnosed myeloma patients should be available next year.

Fig. 29: Daratumumab – Upcoming newsflow (2016)

Compound	Timing	✓	Targeted milestone
Darzalex (daratumumab)	Q1 16	✓	- Launch in the US and other approved territories
	Q2 16	✓	- CHMP decision on monotherapy application
	Q2 16	✓	- Phase III multiple myeloma (MM) interim efficacy analysis in relapsed/refractory MM settings (POLLUX & CASTOR)
	Q3 16		- File for label in relapsed/refractory settings (July-August?)
	H2 16		- Start multiple clinical trials in MM and non-MM indications
	H2 16		- Report initial clinical data in non-MM indications
	Q4 16		- Follow-up data from CASTOR and POLLUX at the 2016 ASH meeting

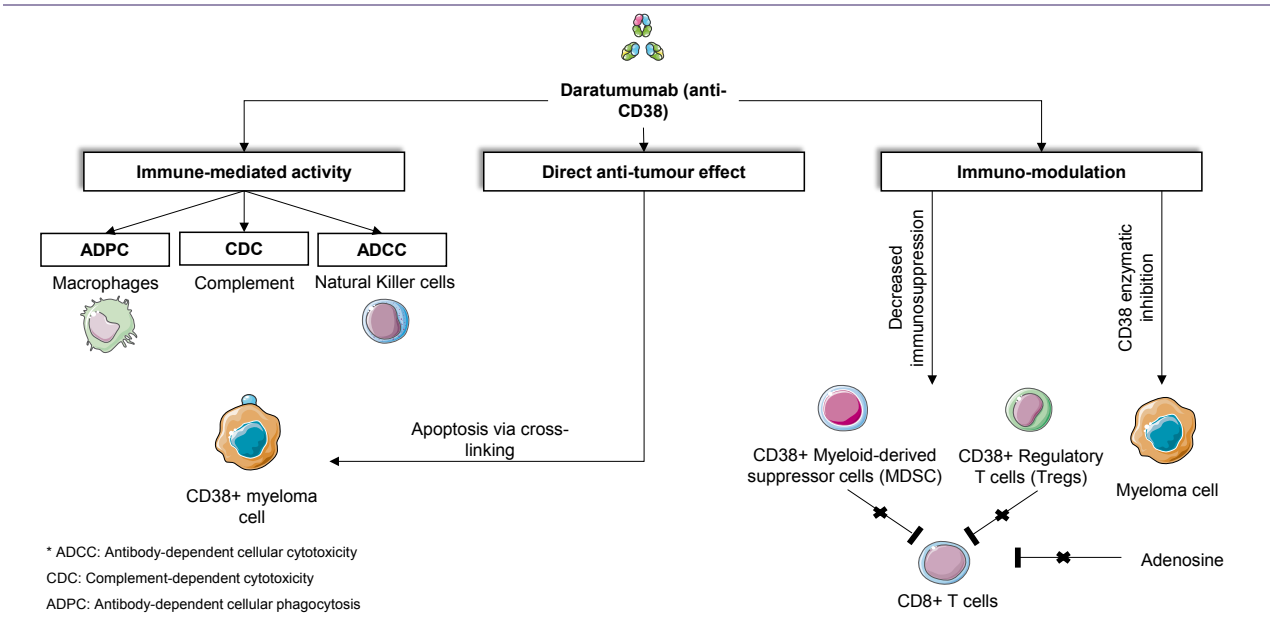
Source: Company Data; Bryan, Garnier & Co ests.

■ **"Dara" or nearly everything one needs for success**

More fundamentally speaking, the Oncology Day along with a recent JNJ's webcast confirmed our view that "dara" is not like other compounds. **We believe that GEN's daratumumab (anti-CD38) is a nice example of what's needed to succeed in the current paradigm of immune-oncology**: 1/ an ability to target different pathways at the same time, including through the modulation of the cancer milieu; 2/ a quite benign safety profile; and 3/ significant synergies with I-O agents and even more conventional treatments (e.g. lenalidomide or bortezomib/carfilzomib). And, in our view, this is why Roche has been quite excited about testing "dara" in combination with atezolizumab in not only myeloma but also solid tumours.

Interestingly, we note that JNJ has recently categorised it as a "myeloid-targeting molecule" together with JNJ-527 (an anti-CSF1R – which is thought to reprogramme tumour-associated macrophages within the TME).

Fig. 30: Daratumumab – Mechanism of action



Source: Genmab; Bryan, Garnier & Co. ests.

Against this backdrop, we believe that other big pharmas will certainly ink some collaboration agreements with JNJ to evaluate "dara" with some of their leading I-O compounds. And among others, we deem AZN as a name that particularly stands out as we see pretty strong synergies between daratumumab and monalizumab (all the more so as the latter could address both liquid and solid cancers).

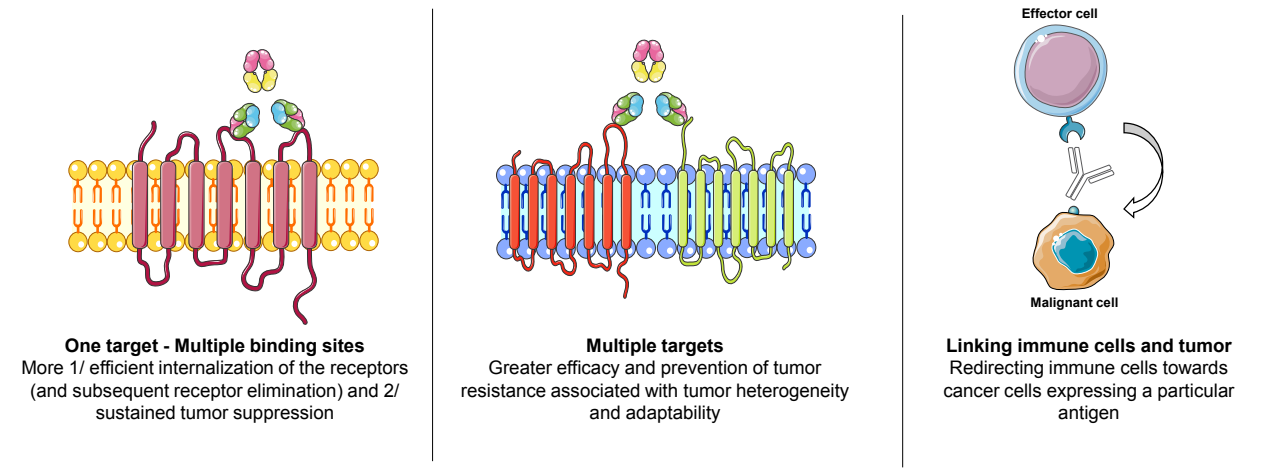
5. Bi-specifics and CAR-T: early promises

5.1. The next wave of innovation

Currently, the vast majority of monoclonal antibodies are "monospecific", with a defined specificity for a given molecular part of one antigen/one epitope… But, as previously seen, these approaches struggle to address the multifactorial state of cancer cells. Combining therapies is obviously an answer, but then their consequent cost is just another issue.

In this context, **bispecific antibodies (bsAbs) are of increasing interest given their ability to simultaneously bind to two different epitopes on the same or on different antigens**… And, as such, they exhibit at least two advantages compared to more traditional mAbs: 1/ they can engage immune effector cells like T-cells, and promote tumour destruction (these types of cells cannot be recruited by conventional mAbs due their lack of Fc receptors); and 2/ they allow the concurrent blockade of two pathways (thus improving the therapeutic efficacy while reducing the risk of resistance formation).

Fig. 31: Bispecifics – How they work



Source: Bryan, Garnier & Co ests.

The very first T-cell engagers that reached the market displayed quite deep response rates in haematological malignancies (see Fig. 32), but many intrinsic factors are impairing their commercial penetration; the main problem being the limited half-life (c. 2 hours for Amgen's Blincyto) and, consequently, the need for continuous infusions, because of their small size and lack of constant domain.

Efforts are thus being made to improve the design of these molecules (e.g. IgG-like with deeper tissue penetration/better interaction profiles, or smaller with increased serum half-life), and/or increase the number of potential bonds.

Fig. 32: Blincyto – Phase II results in adults with R/R ALL

Efficacy endpoints	%
Complete response/complete response with partial hematologic recovery	43%
o/w Complete response (CR)	33%
o/w Complete response with partial hematologic recovery (CRh)	10%
MRD response during first 2 cycles CR/CRh	82%
Hematopoietic stem cell transplant after CR/CRh	40%
. Most frequent grade≥ 3 AE: febrile neutropenia (25%), neutropenia (16%)	
. Serious AE included Cytokine Release Syndrome (CRS) and nervous system AE	

Source: Company Data

5.2. Genmab, Ablynx, Morphosys and Innate Pharma to play the thematic

In our view, small biotechs might be the best vectors to play this theme as their pipeline is much less exhaustive than big pharmas', and as such their valuation is more sensitive to these quite early-stage developments. And within our universe, we believe that Ablynx, Innate Pharma, Morphosys and Genmab are names to be considered.

Fig. 33: Bispecific platforms in our coverage

Company	Clinical stage	Partners	Characteristics
Genmab	Phase I/Preclinical	JNJ, Novartis, Boehringer	IgG1-like bsAbs with similar properties (ADCC, CDC) and clearance rates than wild types
Ablynx	Preclinical	Merck & Co., Boehringer	Albumin-bound nanobodies with extended half-life in spite of their small size
IPH	Preclinical	Sanofi	BsAbs triggering NK cells expressing NKp46 instead of T ones to limit adverse events
Morphosys	Phase I/Preclinical	Emergent Biosolutions	BsAbs linking CD3+ T cells and PSMA expressing cancer cells

Source: Company Data; Bryan, Garnier & Co ests.

5.2.1. Ablynx

Ablynx's nanobodies: small is beautiful

The Belgian biotech developed a Nanobody platform derived from the heavy chain of camelids. The latter has several advantages by 1/ overcoming the limitations of monoclonal antibodies and 2/ offering a wide range of applications.

- Nanobodies have a flexible formatting such as Ablynx is not only able to offer multi-specific constructs (bi-to penta-specific) to enhance potency but could also bind to serum albumin or local anchor protein at the site of the therapeutic target to improve both half-life and localized concentration.

- With a 12 to 15kDa size, a heavy chain antibody is ten times smaller than a conventional antibody (~150kDa) enabling Nanobodies to access cavities into molecular targets and penetrate tissue more effectively.

- They are highly stable so that 1/ they could be stored for over three years in their lyophilized form and 2/ retain more than 80% of their binding activity after one week of incubation at 37°C. This robustness allows for alternative route of administration i.e. inhalation, cream or oral to topical that have the potential to shake up traditional IV administration pathway and notably in IO (inhalation for NSCLC, cream for melanoma?).

- Low immunogenic potential with no Fc region. More than 1,000 patients have been treated in clinical studies and there has been no generalized platform-related immunogenicity which is a safety or pharmacokinetics concern.

This platform already attracted nine pharmaceutical companies through collaboration or partnership agreements of which two major directed towards oncology. Boehringer Ingelheim pushed into phase I its first tri-specific issued from the collaboration. The latter binds to VEGF, Ang2 and serum-albumin. *In vivo* efficacy looks encouraging especially in pancreas and lung cancer (please see here).

While this is an important milestone for Ablynx, it validates above all the rationale of the use of nanobodies in the IO field as well as the company's second collaboration agreement, inked with Merck& Co for a total deal value of USD5.7bn. Not much has been disclosed with regards to the targets so far, however a first milestone paid last year to Ablynx should not be overlooked and is a clear positive signal in our view which implies that nanobodies are at least as good as a combination of antibodies in inhibiting tumour growth. First INDs are expected in late 2016/early 2016 alongside potential update from the big pharma. Fast development time for nanobodies allows for "make and test" approach which fits well in Merck & Co's IO strategy to run several trials for combination therapies.

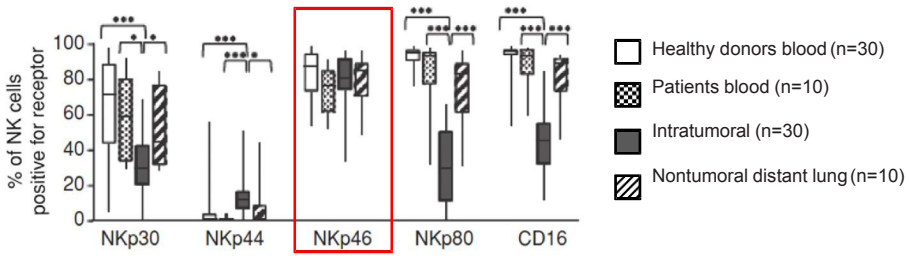
5.2.2. Innate Pharma: leveraging on the NK known-how

Linking NK cells (rather than T ones) to tumours

Innate Pharma has a pretty differentiated approach in this particular field as they develop a bispecific linking NK cells rather than T ones. On paper, these two types of immune cells are equally potent, as they share the same mechanisms of cytotoxicity … But their safety profiles are quite different as NKs have a quite different cytokine-generation profile, and are less likely to trigger severe adverse events like cytokine release syndromes (CRS).

Some might say that other biotech companies are more advanced in the field; but we believe that using NKp46 as a cornerstone to link NK and malignant cells will be a key differentiating factor as 1/ such protein remains expressed at the surface of the immune cells when infiltrate the tumour; whereas 2/ other ones (e.g. CD16) tend to be downregulated.

Fig. 34: Tumour-infiltrating NK cells tend to "retain" NKp46



Source: Platonova et al, 2011

That being said, we also think that some preliminary data involving a proprietary project won't be available before 2017e… And as such, we have decided not to integrate such developments into our SOTP (although the company has already inked a collaboration agreement with Sanofi).

5.2.3. Genmab: "au naturel"

Genmab's duobody platform or how to generate IgG1-like bsAbs

Genmab is also a force to be reckon with as: 1/ the Danish biotech has already inked several collaboration agreements with JNJ, Boehringer Ingelheim and Novartis in the oncology field; 2/ their bispecific compounds seem to benefit from a pretty long half-life (around 25 days) along with a quite potent efficacy profile (one of its dual targeting antibody having proved to be more efficient than two traditional mAbs directed towards the same targets).

In our view, **GEN's competitive advantage lies in its ability to generate IgG1-like bsAbs with similar properties (particularly ADCC and CDC) and clearance rates than wild-type ones**. Plus, preliminary *in vivo* data showed that a proprietary HER2xHER2 could yield a superior activity compared with parental antibody pairs (Labrijn et al, 2013).

5.2.4. Morphosys and MOR209: reasons to believe

MOR209's Phase I data in prostate cancer expected in H2 17

MOR209 is a bispecific linker targeting PSMA and CD3 proteins with an enhanced half-life (around 3-4 days). Although it is early-stage (Phase I), the project could become one of the group's standards in the oncology field given that 1/ we believe that its mechanism makes it very attractive in the treatment of metastatic prostate cancer, 2/ we have identified a single bispecific with a similar construction (BAY2010112 by Bayer), and which is also in Phase I, 3/ competition stems above all from antibodies combined with cytotoxic agents (PSMA ADC by Progenics, ATL101 by Atlab), whose toxicity profiles also seem far from satisfactory.

We understand that some Phase I data should be published by the end of 2017. And based on the data we saw with other current therapies, we would say that MOR209 is only likely to be competitive if the RECIST response rates are close to 35-40% in post-chemotherapy patients and if the percentage of patients having benefited from a reduction in their PSA level of at least 50% works out to 60-65% (bearing in mind that the responses generated by immunotherapies tend to be far more lasting), and if the median survival rate exceeds 20-25 months.

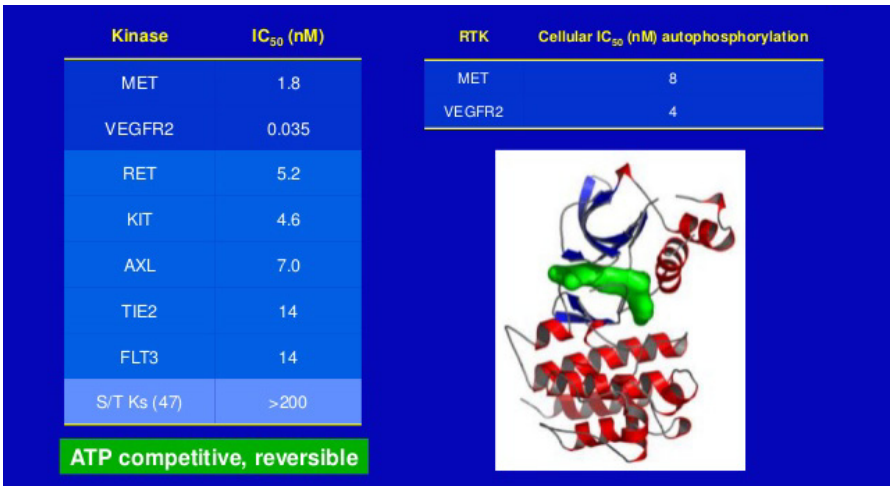
6. Do not restrict yourself to I-O!

In this section, we would like to give an example that was not fully addressed this year at our Oncology Day but is illustrative of the point that targeted therapies should keep a seat in the oncology market, together with IO agents, but should not be fully replaced by them, as also illustrated later with PARP inhibitors.

6.1. Ipsen: cabozantinib makes it a different story

Cabozantinib is a small molecule which inhibits the activity of various tyrosine kinases but, considering the degree of inhibition of enzymatic reaction measured by Ic50 and reported in Fig.2 below, it is fair to say that this multi-kinase inhibitor mainly inhibits VEGFR-2 and MET.

Fig. 35: Measurement of the degree of inhibition of kinases by Cabozantinib



Source: Exelixis

MET could be the differentiating factor

Comparing cabozantinib to other members of the same class, it can be highlighted that a slight difference in the final pharmacological effect might come from the MET inhibition which looks very specific to the drug whereas most, if not all, of the others inhibit VEGR-1/2/3 subgroups, PDGFRβ or c-kit but not MET. However, the MET signalling pathway has been shown to be involved in key processes of cancer growth and dissemination and, maybe more importantly, in resistance to apoptosis.

It is worth noting that cabozantinib is actually already approved in a first indication, although admittedly in a limited one in size called metastatic medullary thyroid cancer (MTC) under the brand name Cometriq, both in Europe and the US. In this rather small indication, Cometriq mainly competes against Caprelsa, a drug that was bought by Sanofi from AstraZeneca last year for USD165m upfront and potential future payments of USD135m. Our understanding is that Ipsen also once competed for these rights but was not ready to pay as much as what Sanofi paid in the end. In 2015, Cometriq achieved EUR4m in sales in the MTC indication in Europe and Ipsen will shortly did it? takeover responsibility for the drug in this indication from Sobi and is therefore likely to book sales as early as Q2 2016. However, it is fair to expect sales reported for Cometriq (or under a new name) to be flat vs 2015, and so somewhere between EUR3m and EUR4m.

Second-line RCC is a key indication for cabozantinib

Clearly this is not where the interest for cabozantinib lies for Ipsen. The key indication is obviously renal cell carcinoma (RCC) in second-line where clinical data have been available to Ipsen before opting-in.

The filing of cabozantinib has already taken place in Europe and feedback from the European Union is expected sometime in the autumn for a global launch starting in Q1 2017.

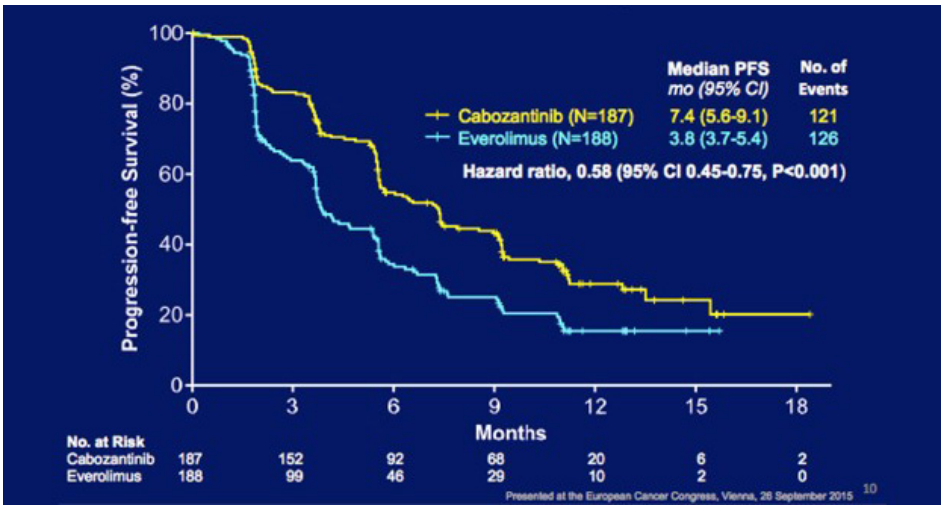
The third indication, and second by order of relevance after RCC, is hepatocellular carcinoma (HCC) where phase III results are expected in 2017 and could add significant potential to the drug.

6.1.1. The key RCC indication

Median PFS meaningfully improved

So RCC is central in Ipsen's decision to buy cabozantinib's rights for ex-US/Japan territories because the comparative trial against everolimus (METEOR) has already delivered robust results that were presented at the ECC/ESMO meeting in Vienna last September with a clear superiority in terms of median PFS, which improved from 3.8 to 7.4 months, as illustrated in Fig.3 (HR=0.58).

Fig. 36: PFS measured by ICR review (METEOR trial)



Source: European Cancer Congress (ECC), Vienna, September 2015

Moreover, if the pre-planned analysis showed a strong OS trend in favour of cabozantinib in the trial, statistical significance was not achieved. But a second interim analysis was performed as agreed with the regulatory authorities and the results showed "a highly statistically significant and clinical meaningful increase in OS for cabozantinib" according to Ipsen. Since then, full data from the METEOR trial have been presented at ASCO 2016 and here are the detailed results:

Fig. 37: OS and PFS by subgroup (METEOR trial)

Subgroup	n	Median OS (months)		OS Hazard Ratio (95% CI)	Median PFS (months)		PFS Hazard Ratio (95% CI)
		CABOMETYX	Everolimus		CABOMETYX	Everolimus	
Number of prior VEGFR TKIs							
1	464	21.4	16.5	0.65 (0.50-0.85)	7.4	3.8	0.52 (0.41-0.66)
≥2	194	20.8	17.2	0.73 (0.48-1.10)	7.4	4.0	0.51 (0.35-0.74)
Only prior VEGFR TKI							
Sunitinib	267	21.4	16.5	0.66 (0.47-0.93)	9.1	3.7	0.43 (0.32-0.59)
Pazopanib	171	22.0	17.5	0.66 (0.42-1.04)	7.4	5.1	0.67 (0.45-0.99)
Prior anti-PD-1/PD-L1 therapy							
No	626	21.4	16.5	0.68 (0.54-0.85)	7.4	3.9	0.54 (0.44-0.66)
Yes	32	Not estimable	16.3	0.56 (0.21-1.52)	Not estimable	4.1	0.22 (0.07-0.65)

Source: American Society of Clinical Oncology (ASCO), Chicago, June 2016

People will compare OS to nivolumab's

So, how do the results compare with those of nivolumab in the CheckMate-025 study? At the time, Opdivo showed a 27% reduction in the risk of death with median OS of 25.0 months compared to 19.6 months with everolimus (p=0.002). In METEOR, cabozantinib showed a 34% reduction in the risk of death with median OS of 21.4 months compared with 16.5 months with everolimus (p=0.0003).

This is a tough question but we would hypothesise that given the excitement around I-O, nivolumab could be a preferred option anyway. That said, can the route of administration make a difference? What about price? At this point, it does not look possible to stratify patients with either of the two drugs to determine higher responders and so physicians are unlikely to make a decision based on epidemiology or based on any tumour testing.

In the end, as the disease progresses, maybe safety and quality of life will be given priority. From that perspective, it remains to be seen which of the two will be preferred as the section on the prescribing information of Opdivo referring to RCC reports a discontinuation rate of 16%, a 44% rate of drug delays due to side-effects (competitive with the 60% rate of dose reduction with "cabo"?) and a 47% rate of serious adverse reactions in patients receiving Opdivo. So the difference may not be so huge as suggested in the *NEJM* in September 2015.

What if nivolumab moves in first-line?

There is another unknown factor obviously which is: what happens if the ongoing phase III CheckMate-214 is positive? This one is testing the IO/IO combination of nivolumab with CTLA-4 targeting agent ipilimumab in the first-line setting of RCC in comparison with the current standard of care sunitinib (Sutent). PFS and OS are co-primary endpoints. If positive, despite the very high price, it is likely to become the new standard in first-line RCC. If so, what would happen in second-line? Which VEGFR-based therapy would qualify as the standard?

It looks like I-O will take an (yet) undefined seat in the RCC market, between first- and second-line. So, cabozantinib, with potential best-in-class survival data, may have to compare with current leaders (i.e. Inlyta, Votrient or Sutent) to increase its legitimacy as a second-to-IO agent in RCC. This could mean extra R&D costs as it is not covered by the existing agreement with Exelixis.

However, a NCI (National Cancer Institute)-sponsored phase II trial called CABOSUN is also ongoing to test cabo against Sutent in 1L RCC in first-line therapy of intermediate or poor risk patients per standard risk classification. Enrolment of 150 patients was completed in March 2015 and the headline results were reported earlier than anticipated in late May 2016. We therefore know that CABOSUN achieved its primary endpoint, i.e. PFS improvement when comparing cabozantinib to sunitinib in 1L knowing that the trial was powered to detect at least a 33% difference compared to a drug whose prescribing information points to a median PFS of 47.3 weeks (about 11 months). Because the trial is limited in size (150 patients) and open-label, we would not suggest that 1L will be addressable shortly but, undoubtedly, it is going to help influence physicians' decisions. Exelixis will finance a phase III trial in 1L and Ipsen will then have the right to opt-in at the beginning or at the end.

In the end, Ipsen is likely to oppose BMS with nivolumab but also Pfizer (Inlyta, Sutent – which has just reported positive results in adjuvant RCC) and Novartis (Votrient). So the bar is high but we find the data package quite compelling so far in RCC and to say the least quite competitive as well. Roche is also very likely to join the fight here as representatives at our Oncology Day were very excited about the opportunity to develop atezolizumab in combination with Avastin in RCC in 1L. Phase III study IMmotion151 is expected to report results in 2017, making 1L definitely difficult to reach for cabozantinib except maybe in specific subgroups. For instance, data presented at ASCO in patients with both bone and visceral metastases were outstanding, with median PFS jumping from 2.7 to 7.4 months and median OS progressing from 12.1 to 20.1 months.

Another strategy for sure can be a combination of cabozantinib and a PD-1/PD-L1 targeting agent, although this is years from delivering data. By then, we would assume that 2L would the most reasonable space where cabozantinib should sit (all the more so that METEOR says that cabozantinib could have even greater results when used after anti-PD-1/PD-L1 therapy), except if regulators stratify the target market and limit the use of PD-1/PD-L1-based therapies to quick responders.

EUR200m peak sales looks achievable with conservative assumptions

In conclusion, we assume "cabo" can reach the EUR200m mark in Europe (+Australia) which Ipsen alluded to during its conference call with the single RCC indication by the middle of the next decade (see Fig.X). The key assumptions when building our sales model have been a mid-range in the estimated addressable market of 15-25% of the 110,000-115,000 patient population, a market share growing upwards to 25% (Afinitor to which Cabozantinib has been compared holds about 20% currently in Europe), an annual price of EUR60,000 which is factored in only over the period of the median PFS that we took for 9 months assuming 2L will form the majority of the prescriptions.

The price we opted for looks like a balanced estimate when considering Inlyta (EUR43,800 per year in France) on one side and Opdivo on the other (around EUR100,000 per year across the various indications in Europe), whereas a premium is likely over the price so far set for Cometriq sold as a capsule formulation for MTC (EUR4,600 per month) when RCC and HCC will be available in a tablet form.

Fig. 38: Cabozantinib – sales model in MTC+RCC

	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
Prevalence Europe RCC	110 000	111 100	112 211	113 333	114 466	115 611	116 767	117 934	119 114	120 305	12 1508	122 723
5% extra prevalence for ROW	5 500	5 555	5 611	5 667	5 723	5 781	5 838	5 897	5 956	6 015	6 075	6 136
Addressable patients (20%)	23 100	23 331	23 564	23 800	24 038	24 278	24 521	24 766	25 014	25 264	25 517	25 772
Market share	0	2%	6%	10%	14%	17%	20%	23%	25%	25%	25%	25%
Volume	0	467	1 414	2 380	3 365	4 127	4 904	5 696	6 253	6 316	6 379	6 443
PFS median	0,75	0,75	0,75	0,75	0,75	0,75	0,75	0,75	0,75	0,75	0,75	0,75
Annual price	60 000	60 000	60 000	60 000	60 000	60 000	60 000	60 000	60 000	60 000	60 000	60 000
Price x PFS	45 000	45 000	45 000	45 000	45 000	45 000	45 000	45 000	45 000	45 000	45 000	45 000
Sales in MTC	3 000	4 000	4 500	5 000	5 000	5 000	5 000	5 000	5 000	5 000	5 000	5 000
Total Sales MTC+RCC	3 000	24 998	68 124	112 100	156 439	190 729	225 690	261 331	286 407	289 221	292 064	294 934

Source: Bryan, Garnier & Co ests.

These are the numbers we are factoring into our sales model.

Circa 15% royalty rate on sales

This will go together with the calculation of royalties on sales to be paid to Exelixis by Ipsen in various tranches which will represent, when the drug gets mature in the RCC indication, about 15% of sales on average, i.e. EUR30-35m per annum in the middle of the next decade.

Fig. 39: Cabozantinib – royalty model in MTC+RCC

Royalties (USD,000)	2016e	2017e	2018e	2019e	2020e	2021e	2022e	2023e	2024e	2025e	2026e	2027e
2%	67	425	1 117	1 000	1 000	1 000	1 000	1 000	1 000	1 000	1 000	1 000
12%			3 021	8 844	18 000	18 000	18 000	18 000	18 000	18 000	18 000	18 000
22%					4 977	13 301	21 788	30 441	36 528	37 211	37 901	38 598
26%												
Total royalties (USD, 000)	67	552	4 524	9 844	23 977	32 301	40 788	49 441	55 528	56 211	56 901	57 598
Total royalties (EUR, 000)	**60**	**500**	**4 100**	**8 921**	**21 729**	**29 273**	**36 964**	**44 805**	**50 322**	**50 941**	**51 567**	**52 198**
As a % of sales	2%	2%	6%	8%	14%	15%	16%	17%	18%	18%	18%	18%

Source: Bryan, Garnier & Co ests.

Although the mechanism of commercial milestones is less precise, we have assumed that a first one would be reached when the drug achieves USD100m, which represents about USD25m, i.e. 5% of the total USD545m milestones to be paid to Exelixis contractually if all thresholds are exceeded (the last one would be paid if cabozantinib achieves blockbuster status in Ipsen's territories).

Should Ipsen have to pay Exelixis more commercial milestones, this means we would have to revise our sales estimates upwards.

In conclusion, we expect Opdivo and Tecentriq to take a meaningful part of the RCC market but there are limiting factors to their use, including response rate and price. We therefore expect European regulators to listen to the cabozantinib proposition made by Ipsen. The financial terms that formed the base of the agreement with Exelixis are balanced in our view and mainly rely on a success in 2L RCC, which appears reasonable based on available data.

6.1.2. HCC to be seen as a free option

The third indication cabozantinib is very much engaged in is the second-line of treatment of advanced hepatocellular carcinoma (HCC). Although it is far from the first, HCC is however the sixth most common malignancy and the third in terms of mortality worldwide (with a predominance in Southern Asia) and one of the poorest if we consider the way it is addressed from a pharmacological perspective. Despite several attempts, very few drugs have proven any efficacy in this disease.

Despite modest efficacy, the current standard in first-line is Bayer's sorafenib (Nexavar), whereas no approved drug is available for more advanced treatment lines.

Interesting early data for nivolumab in HCC

However, the same players as in RCC are currently trying to make inroads into this setting where there is a clear unmet medical need and so a meaningful potential return for healthcare companies: within the small molecules space, it looks like MET inhibition is the most interesting pathway whereas I-O can be (once again) disruptive when first (although very early-stage) data are considered. In a first phase I/II trial in 42 evaluable patients presented at ASCO in May 2015, nivolumab (again) showed a 20% response rate with a fairly long duration of response and a 48% stabilisation rate. The 12-month survival rate was 62% at the level of the entire population of the study where it is usually about half for those treated with sorafenib in first-line.

A first-line HCC phase III called CheckMmate-459, comparable to sorafenib, had already started enrolling in late 2015 with an estimated total number of patients at 726 and a target date for primary outcome measures in July 2017. The co-primary endpoints are TPP and OS, whereas the secondary endpoints are ORR and PFS. Obviously, these results will be not only of high significance for nivolumab but also for all drugs currently in development in HCC, be it in first- or second-line. And they will be made available after cabozantinib's phase III results in second-line but before it is approved, so it will potentially impact it before it can get any fruit from this indication.

MET inhibition looks interesting in HCC

That said, let's see how cabozantinib could play out in this disease. First, it looks fair to say that a lot of different approaches have failed to demonstrate any benefit in HCC, and even sorafenib's efficacy is considered very modest. So molecules sharing more or less the same targets with sorafenib may not necessarily attract high interest from the medical community. However, what we said for RCC may even apply with more accuracy in HCC, i.e. that the MET component in cabozantinib's TK activity is key. Evidence has emerged and is improving that dysregulation of the HGF-cMET pathway is implicated in HCC carcinogenesis and progression, hence the interest for MET inhibition in this setting.

Two MET tyrosine kinase inhibitors have presented phase II data which are encouraging and deserve further investigation.

The first is a highly selective MET inhibitor called tivantinib, developed by ArQule and Daiichi Sankyo which, however, demonstrated in phase II that its activity was limited to high MET expressers. In this subgroup, median TTP, PFS and OS were all statistically significant and, as a consequence, the sponsors have designed a phase III study with a twice-daily 240mg dose in MET-high HCC patients only (20% to 48% of the total population, depending on the source). The pre-planned sample size is 300-400 patients who have either progressed on or been intolerant to sorafenib. The study is ongoing and the completion date is expected during 2017. OS is the primary endpoint.

Encouraging rate of disease control in phase II

The second is precisely cabozantinib which is a less selective MET inhibitor and has been tested in a wide range of subjects with various advanced solid tumours. Among them, 41 had advanced HCC and Child-Pugh class A (classification that assesses the functional capacity of the liver), with half of them being naïve to any treatment and the other half having received prior sorafenib-based therapy. Over the 36 patients evaluable for tumour assessment at week 12, the overall disease control rate was 68%, including two partial responses (+one that came later).

Based on these results, Exelixis decided to start a phase III trial (called CELESTIAL) which is due to enrol about 760 patients with advanced HCC who have received sorafenib in first-line. Unlike tivantinib, participants are not stratified based on MET expression. The suggestion by Exelixis is that MET is involved but may not be the sole pathway to influence response and efficacy. The trial is ongoing at the same daily oral dose as in RCC, i.e. 60mg which by the way is a reduction compared to the 100mg dose tested in phase II. The results are expected to be reported towards the turn of the year, more likely in early 2017.

We thought that cabozantinib would be next to report phase III results and so, if positive, it may well have taken the lead in second-line HCC. That said, considering the history in this field, the limited sample size in phase II, the dose reduction implemented while entering phase III, the absence of patient stratification, we have applied a low PoS to the drug in HCC also because tivantinib and more importantly nivolumab phase III data are very likely to impact the treatment paradigm too. As a consequence, we had decided not to factor any sales in HCC for cabozantinib into our model yet. And we were right because, since then, in late June, investigators of the RESORCE phase III trial presented data at the WCGC congress in Barcelona resulting in regorafenib (Stivarga, Bayer) disclosing data making it the likely new SoC in 2L HCC as it improved median PFS from 1.5 to 3.1 months and median OS from 7.8 to 10.6 months vs placebo. Stivarga is also a MKI with a wide-ranging profile of tyrosine kinase inhibition and it is very difficult to try extrapolate what it says, if anything, for cabozantinib in the same indication.

HCC not in our model (yet)

So, again, 2L HCC is not factored into our sales estimates at all. Ipsen also refers to 2L HCC as "more challenging" an indication, that would be a "bonus" if successful, worth EUR50-150m in terms of market opportunity.

6.2. What about DDR?

As we make this update in oncology, we believe it is fair to ride also somewhat outside the scope of what was covered during our Oncology Day at Curie and to address topics that we believe are as hot as immuno-oncology, although they are outside this field. One of these could be CDK 4/6 inhibition which looks very promising in breast cancer but we've decided to talk about DNA Damage Repair (DDR) because recent data suggest a strong effect in ovarian cancer that could be extrapolated to other tumour types such as breast and maybe prostate cancer with, if so, very high cumulated sales potential in the end.

6.2.1. Outstanding results for niraparib in ovarian cancer

Phase III data with niraparib in ovarian cancer exceeded all expectations

Obviously very recently unveiled phase III data in ovarian cancer by Tesaro with niraparib exceeded the most optimistic scenarios. The drug achieved PFS endpoints in all pre-specified three populations of germline BRCA mutant OC, and non-germline BRCA mutant either HRD-positive or all comers.

A PFS multiplied by 3 to 4

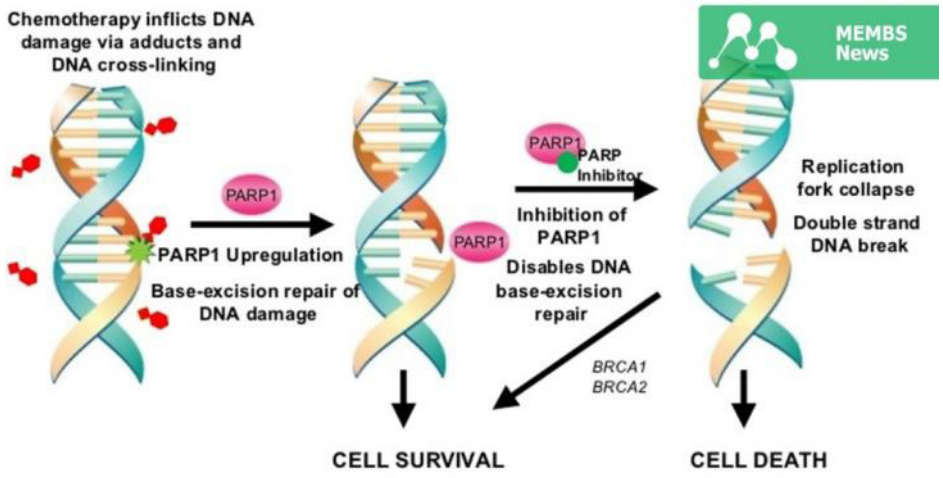
Although Tesaro set a high level for statistical significance, all endpoints were easily reached with p values below 0.0001 and HR ranking between 0.27 and 0.45. Presented in number of months, median PFS was almost quadrupled from 5.5 to 21 months in gBRCA ovarian cancer patients, whereas in non-gBRCA it was brought from 3.8-3.9 months up to between 9.3 and 12.9 months. As in previously disclosed studies, NOVA showed similar safety concerns, i.e. of an haematological nature with thrombocytopenia, anaemia and neutropenia being most frequently reported grade 3-4 side-effects with incidences of 28%, 25% and 11% respectively. The discontinuation rate was 14.7% for niriparib compared to 2.2% with placebo.

6.2.2. How do PARP inhibitors work?

PARP inhibitors have been developed to try to interfere with the natural DNA damage repair (DDR) system within all individuals which also benefits cancer cells when attacked by other therapeutics like chemotherapies. Now (cancer) cell death requires a double-strand DNA break which is more difficult to obtain and explains why BRCA-1 and BRCA-2 mutated cancers are prioritised because it has been observed that the HR (homologous recombination) pathway in these cancers was already impaired (secondary to germline mutation in one copy or loss of heterozygosity inactivating or removing the other copy). PARP inhibitors act by targeting the base excision repair pathway (BER) which consists of recruiting other repair proteins to the site of DNA damage and so when both pathways are disrupted then the cell is more likely to die. Note at this point that one specific cancer type is very similar to BRCA-mutated cancers although it does not harbour a mutation (sometimes called BRCAness phenomenon) which is TNBC (triple negative breast cancer), explaining why PARP inhibitors are also developed in this setting with some initial signs of strong activity.

Another potential mechanism of action of PARP inhibitors is called PARP trapping and suggests cytotoxic activity of the drugs in this class. The concept is that PARP inhibitors trap the recruited PARPs with the DNA-damaged sites and prevent dissociation between the two, thus prohibiting the cell's ability to replicate and again promoting its death.

Fig. 40: How PARP inhibition works



Source: MEMBS (Middle East Molecular Biology Sources)

6.2.3. AstraZeneca and Tesaro lead the race in ovarian cancer

Two PARP inhibitors are of particular interest for us

Returning to the field of PARP inhibitors, there are actually five that are well identified and in late-stage clinical development. Beyond Tesaro's niraparib which is now strongly supported by the NOVA phase III trial's results in ovarian cancer, summarised above, two other PARP inhibitors are of particular interest to us:

- First is AstraZeneca's first-in-class product olaparib which is already marketed under the brand name Lynparza in a fairly narrowed indication of highly-advanced metastatic epithelial ovarian cancer after the failure of several other lines of treatment. Reported sales were USD44m in Q1 2016;

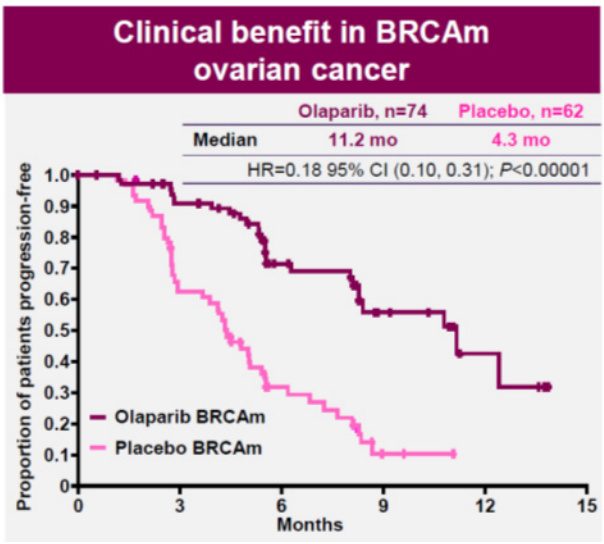
- Second is Medivation's talazoparib because Sanofi has made an offer to acquire the company and the PARP inhibitor is central to the investment case as it would participate strongly in the strengthening of Sanofi's pipeline of in oncology which is described as a strategic field in which the group intends to rebuild a strong presence.

Again, because cells harbouring mutations or deficiencies in homologous recombination, i.e. cells with BRCA1/2 mutations, are more particularly likely to benefit from the cytotoxic effects of PARP inhibitors as these cells more often present double-strand breaks inaccurately repaired, solid tumours with BRCA mutations are prioritised cancer types on which PARP inhibitors are tested and where they are more clinically advanced. That said, the initial findings in prostate cancer also look very promising for the class, as illustrated by the BTD granted to olaparib in this setting by the FDA.

AZN and Tesaro are leading the race in ovarian cancer

Starting with ovarian cancer, which is the prime indication of first-in-class product Lynparza, it looks like AstraZeneca and Tesaro are leading the pack here. On one hand, Lynparza is already approved but in a niche indication, whereas Tesaro's drug achieved stellar results in a phase III trial called NOVA that could open up access to a much larger patient pool.

Fig. 41: Study 19 phase II results with olaparib



Source: Company Data; Bryan, Garnier & Co ests.

A lot of phase III data available soon

While Lynparza is so far only approved on the basis of a phase II single-arm trial (known as study 19, see Fig. 38) in already highly treated patients with ovarian cancer, NOVA recruited more than 500 patients in a setting known as "maintenance therapy" where patients do respond to initial platinum-based chemotherapy but who are tested for benefit when niraparib is added.

Of course, Lynparza has embarked in several phase III trials in ovarian cancer in the SOLO programme and two of these should report results fairly soon, i.e. by early 2017:

- SOLO-1 aims at recruiting about 400 patients and is very similar to NOVA by design as patients to be included in the trial will have to be in partial or complete response to previous platinum-based therapy. Unlike phase II study 19, which tested a 400 mg twice-daily dose, SOLO-1 phase III trial will test 300 mg as twice-daily dose (2x 150 mg tablets) with a dose reduction to 250 mg and even 200 mg possible in the case of documented toxicity. PFS is the primary endpoint and the primary completion date is expected to take place in February 2017 according to clinicaltrials.gov.
- SOLO-2 aims at recruiting close to 300 patients and differs from SOLO-1 mainly in that patients recruited must have completed two or more lines of platinum-based therapies and where the disease has come back.

The results of both studies could be reported by year-end (SOLO-2 more likely than SOLO-1) and at the latest in Q1-2017 with filing shortly thereafter. Tesaro said that it would file the NOVA results in Q4-2016.

So, in ovarian cancer, we see the two drugs as well positioned to share the target market, considering that about 15% of ovarian cancers are BRCA mutated. Obviously, moving to earlier stages of treatment would significantly increase the target population and the average duration of treatment (up to 21 months PFS in NOVA vs 11 months in study 19). The price might slightly go down but it is likely to remain in the same bracket as other recently-launched innovative cancer therapies, i.e. about USD50,000-75,000 in Europe and about twice as much (list price) in the US. We believe BRCA-mutated ovarian cancer is in total a USD1-1.5bn opportunity for PARP inhibitors.

It is also worth noting that some phase II trials have already started to combine PARP inhibitors with VEGF targeting agents like bevacizumab (AVANOVA trial is nira + beva) or cediranib (ola + cedi), both in recurrent platinum-sensitive ovarian cancer. Although oral is the preferred option, we see beva as the more reasonable choice given its history of use in this setting. Note also that some PD1/PD-L1 targeting agents are being investigated in ovarian cancer too, which may also participate in a paradigm shift (Pfizer recently announced that it has entered into a second phase III with avelumab), as well as another DDR approach, namely WEE-1 inhibition (phase II in combination with Lynparza for AZD1775 started in Q1 2015 for instance).

6.2.4. The game is more open and competitive in breast cancer

Moving to breast cancer now, PARP inhibitors are also expected to play a significant role as this is another type of malignancy frequently associated with BRCA mutation (said to be about 10% in breast) and also because early evidence of activity has already been achieved in trials. Moreover, 15 to 20% of breast cancers are reported as "triple negative" and these also should benefit from PARP inhibition. After trying to avoid double accounting, we would assume that about 20 to 25% of breast cancers could be targeted by PARP inhibitors. Of course, it remains to be demonstrated that these agents can be equally effective whatever the stage of the disease or the therapy setting, meaning whether it is metastatic, neo-adjuvant or adjuvant breast cancer.

Maybe because the opportunity is larger, there is a much fiercer competition among PARP inhibitors than in ovarian cancer and almost all participants are already embarked in phase III clinical trials. Again we find AstraZeneca's olaparib in two studies in metastatic and adjuvant BC and Tesaro's niraparib in metastatic BC, but also AbbVie's veliparib in neo-adjuvant and metastatic BC as well as in TNBC and Medivation's talazoparib in metastatic BC.

2017 likely to be the key year to get data in breast cancer

Starting with the metastatic BC setting for which clinical data should come first, we summarise below the key players involved in the battle with the related clinical trials:

Compound	Study	Investigational arm	No. of patients	Primary Completion Date
Olaparib	OlympiAD	Monotherapy	310	August 2016
Veliparib	NCT'694	+ CarboTax	270	January 2017
Talazoparib	EMBRACA	Monotherapy	429	June 2017
Niraparib	BRAVO	Monotherapy	306	September 2017

Sources: BMC Medicine (2015), clinicaltrials.gov.

So far we have adopted a step-by-step quite cautious approach with the only PARP inhibitor that was of relevance for our coverage universe, i.e. Lynparza (AstraZeneca). We assume USD650m peak sales potential for the drug in ovarian cancer in 2020 and take a 30% probability of success (PoS) in metastatic breast cancer (MBC). Overall, this translates into USD1.0bn sales for Lynparza in 2022. We would be surprised not to be on the safe side with these kinds of numbers for Lynparza even though it is fair to wait for more clinical data in ovarian and breast before we adopt a more optimistic stance. We also have to factor in the fierce competition from Tesaro (now more likely to be acquired by a larger player?) and maybe from others including Medivation that, if acquired by Sanofi or another contender like Pfizer, will benefit from deep pockets to invest behind talazoparib. In the end, the class is likely to be bigger than we have expected so far but with a higher number of large players involved.

We are also interested in learning more about how PARP inhibitors (and other DDR types of approaches like WEE-1 inhibitors) can interact with other targeting agents like CDK4/6 in breast, with chemotherapies and with IO agents because this will tell a lot about how they are going to be used, when and how long. It is somewhat too early to tell.

BRYAN, GARNIER & CO

INDEPENDENT RESEARCH UPDATE

13th July 2016

AstraZeneca

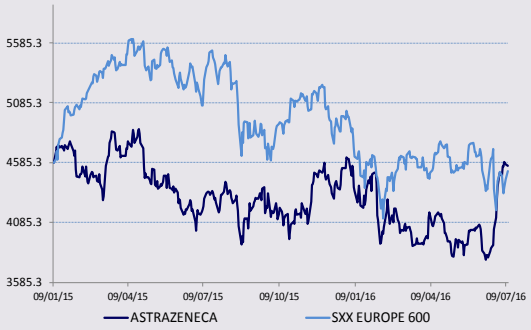
Buying time

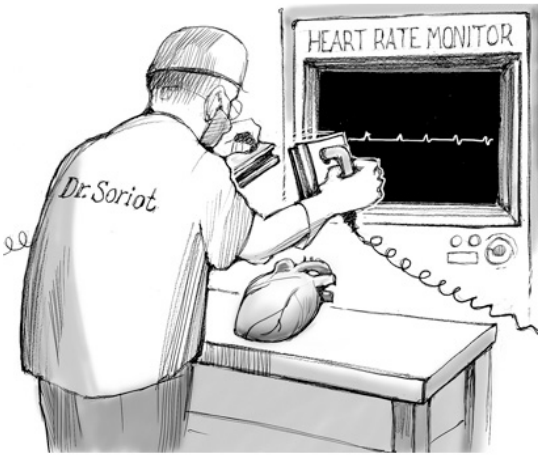
Healthcare

Fair Value 5370p vs. 5100p (price 4,476p) **BUY**

Bloomberg	AZN LN
Reuters	AZN.L
12-month High / Low (p)	4,628 / 3,774
Market capitalisation (GBPm)	56,604
Enterprise Value (BG estimates GBPm)	68,227
Avg. 6m daily volume ('000 shares)	2,845
Free Float	100%
3y EPS CAGR	-3.3%
Gearing (12/15)	48%
Dividend yield (12/16e)	4.74%

YE December	12/15	12/16e	12/17e	12/18e
Revenue (USDm)	23,641	21,272	20,402	21,474
EBIT (USDm)	4,114	3,047	5,219	5,267
Basic EPS (USD)	2.24	1.39	2.83	2.87
Diluted EPS (USD)	4.26	3.63	3.82	3.86
EV/Sales	3.53x	4.23x	4.51x	4.39x
EV/EBITDA	14.1x	21.2x	15.1x	14.5x
EV/EBIT	20.3x	29.5x	17.6x	17.9x
P/E	13.8x	16.3x	15.4x	15.3x
ROCE	16.2	13.5	12.1	12.0





AstraZeneca is not yet in a comfortable situation overall as innovative drugs do not yet offset the patent cliff and it is uncertain whether the group will be able to show any growth before 2018. However, in oncology, which is the focus of this report, things are developing well: Lynparza and Tagrisso are taking off nicely, key data read-outs are coming for durva and treme next year and acalabrutinib should soon be added to the list of key drugs for the company.

- We see sales in oncology doubling in size from 2015 to 2019 and tripling by 2022 for AstraZeneca despite using still cautious PoS when making our forecasts.

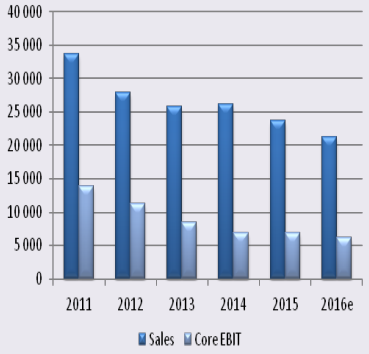
- In this report, we pay particular attention to ICI (immune checkpoint inhibitors) including durvalumab but we also and more specifically address two non-IO drugs: PARP inhibitor Lynparza (in ovarian and breast cancers) and BTK inhibitor acalabrutinib (in liquid tumours). We are taking the opportunity of this report to include Acerta for the first time in our model, meaning debt attached to the acquisition (including upfront and unconditional payment) but more importantly estimated future sales that are risk-adjusted by indication. Although six different indications are factored in, our risk-adjusted peak sales of USD2.1bn in 2026 mainly derives from R/R and 1L CLL where it may achieve USD1.8bn in sales. Phase III data in R/R CLL are expected to be released by year-end.

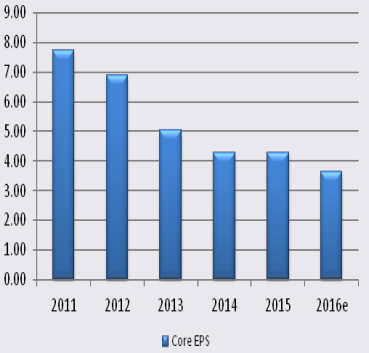
- As for Lynparza, we see the drug as mainly competing with Tesaro's in ovarian cancer while the game is more open in the breast cancer area which can be much bigger but with many more compounds engaged including potential best-in-class talazoparib (Medivation). What is clearer now is that, since Tesaro disclosed data recently with its own candidate, the class looks highly attractive at least in these two cancers.

- Last but not least, durvalumab is likely to deliver clinical data in head & neck and, with the MYSTIC trial over the coming 12 months, we see the two settings as key for the peak sales of the drug that is so far not clearly differentiated from the pack. We have 50% PoS on USD3.7bn PS.

Analyst:
Eric Le Berrigaud
33(0) 1 56 68 75 33
eleberrigaud@bryangarnier.com

Sector Analyst Team:
Mickael Chane Du
Hugo Solvet





Company description

AstraZeneca was formed in 1999 by the merger of Swedish Astra and British Zeneca. Originally a life science company, it then span off its agrochemicals business (merged with Novartis' to form Syngenta) and focused on pharmaceuticals, divesting some other minor diversifications and acquiring biotech capabilities with CAT and then MedImmune. AstraZeneca has strong brands like Nexium, Crestor or Seroquel and is currently facing a deep patent cliff. Time will tell whether R&D revives and is able to deliver new medicines that could offset part if not all of sales lost to patent expiries.

Profit & Loss account (USDm)	**2013**	**2014**	**2015**	**2016e**	**2017e**	**2018e**
Sales	25,712	26,095	23,641	21,272	20,402	21,474
Change (%)	*-7.7%*	*1.5%*	*-9.4%*	*-10.0%*	*-4.1%*	*5.3%*
EBITDA	7,850	4,104	5,937	4,248	6,073	6,500
EBIT	3,712	2,137	4,114	3,047	5,219	5,267
Change (%)	*-54.4%*	*-42.4%*	*92.5%*	*-25.9%*	*71.3%*	*0.9%*
Core EBIT	8,390	6,937	6,902	6,142	6,409	6,457
Change (%)	*-24.8%*	*-17.3%*	*-0.5%*	*-11.0%*	*4.3%*	*0.7%*
Financial result	(445)	(891)	(1,045)	(1,042)	(945)	0.0
Pre-Tax profit	3,267	1,246	3,069	2,005	4,274	4,366
Exceptionals	0.0	0.0	0.0	0.0	0.0	0.0
Tax	696	11.0	243	276	718	735
Income from associates	0.0	0.0	0.0	0.0	0.0	0.0
Minority interests	15.0	2.0	1.0	(30.0)	(20.0)	5.0
Reported net result	2,556	1,233	2,825	1,759	3,576	3,626
Core Net result	6,319	5,396	5,390	4,587	4,829	4,879
Change (%)	*-27.0%*	*-14.6%*	*-0.1%*	*-14.9%*	*5.3%*	*1.0%*
Cash-Flow Statement (USDm)						
Operating cash-flows	7,348	4,260	3,496	2,752	4,364	4,763
Change in working capital	172	(3,080)	(351)	537	763	62.5
Capex (net)	2,023	2,752	2,788	1,400	1,400	1,200
Financial investments	1,158	3,804	2,446	3,139	0.0	1,500
Dividends paid	3,507	3,545	3,486	3,539	3,539	3,539
Net Debt	1,162	4,504	8,823	15,323	17,361	19,670
Free Cash flow	4,317	173	(2,955)	(2,324)	2,201	2,001
Balance Sheet USDm						
Shareholder funds	23,253	19,646	18,509	15,262	13,673	12,470
+ Provisions	3,650	4,058	3,216	3,216	3,216	3,216
+ Net Debt	1,162	4,504	8,823	15,323	17,361	19,670
= Invested Capital	28,065	28,208	30,548	33,801	34,250	35,356
Tangible assets	33,697	40,786	43,210	45,299	44,349	44,699
+ Working Capital	1,827	(1,253)	(1,604)	(1,067)	(305)	(242)
+ Others / Miscellanous	(7,459)	(11,325)	(11,058)	(10,431)	(9,794)	(9,101)
= Capital employed	28,065	28,208	30,548	33,801	34,250	35,356
Total Balance Sheet	55,899	58,595	60,124	54,870	51,570	49,996
Financial Ratios						
Operating margin	14.44	8.19	17.40	14.32	25.58	24.53
Core operating margin	32.63	26.58	29.20	28.87	31.41	30.07
Tax rate	20.28	16.15	7.92	7.92	20.99	21.45
Net margin	9.78	2.29	6.84	1.26	9.44	10.76
ROE (after tax)	10.76	2.91	8.61	1.73	13.48	17.87
ROCE (after tax)	19.86	15.60	16.16	13.48	12.13	12.03
Gearing	5.00	22.93	47.67	100	127	158
Distribution rate	137	287	125	201	98.97	97.59
Number of shares (diluted)	1,250	1,263	1,264	1,264	1,264	1,264
Per share data USD						
Reported EPS	2.04	0.98	2.24	1.39	2.83	2.87
Restated EPS	2.04	0.98	2.24	1.39	2.83	2.87
Core EPS	5.05	4.28	4.26	3.63	3.82	3.86
change (%)	*-26.5%*	*-15.3%*	*-0.3%*	*-14.9%*	*5.3%*	*1.0%*
Goodwill per share	0.0	0.0	0.0	0.0	0.0	0.0
NPV	18.58	15.54	14.63	12.04	10.76	9.79
Cash flow per share	5.88	3.37	2.77	2.18	3.45	3.77
FCF per share	3.45	0.14	(2.34)	(1.84)	1.74	1.58
Dividend per share	2.80	2.80	2.80	2.80	2.80	2.80

Source: Company Data; Bryan, Garnier & Co ests.

BRYAN, GARNIER & CO

INDEPENDENT RESEARCH UPDATE

13th July 2016

Ipsen

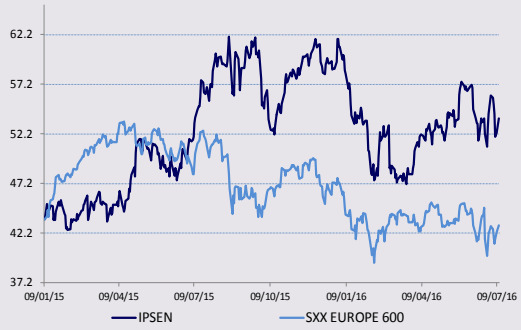
Oncology is an increased focus

Healthcare

Fair Value EUR64 vs. EUR63 (price EUR53.30) **BUY-Top Picks**

Bloomberg	IPN FP
Reuters	IPN.PA
12-month High / Low (EUR)	62.0 / 47.1
Market capitalisation (EURm)	4,437
Enterprise Value (BG estimates EURm)	4,525
Avg. 6m daily volume ('000 shares)	88.00
Free Float	32.0%
3y EPS CAGR	13.7%
Gearing (12/15)	-8%
Dividend yield (12/16e)	1.59%

YE December	12/15	12/16e	12/17e	12/18e
Revenue (€m)	1,444	1,568	1,715	1,865
EBIT (€m)	322.48	341.94	390.52	465.61
Basic EPS (€)	2.31	2.81	3.09	3.76
Diluted EPS (€)	2.78	2.90	3.40	4.09
EV/Sales	3.00x	2.89x	2.59x	2.29x
EV/EBITDA	11.8x	11.1x	9.6x	7.9x
EV/EBIT	13.4x	13.2x	11.4x	9.2x
P/E	19.2x	18.4x	15.7x	13.0x
ROCE	22.6	17.7	19.6	22.8



With David Meek appointed as new CEO, Ipsen is moving one step closer to an oncology-focused company. Under this new leadership, we expect Ipsen to make another transforming deal in the field of oncology, this time including US rights to build on Somatuline's success there. This should make the story even more attractive.

- Decapeptyl was the cornerstone, Somatuline is the growth driver and Cabometyx is still debated but could be a good surprise.

- Of course, in the context of the emergence of IO therapies, the feeling is that PD-1/PD-L1 agents will take the lion's share of most of the non-hormone dependent cancers. Indeed, Opdivo reported very good results in RCC, whereas Pfizer and Roche look very excited and are moving quickly to develop combinations of avelu/Inlyta and atezo/Avastin respectively. However, assuming IO takes most of 1L RCC, this leaves significant room for cabo in 1L sub-segments (like in advanced stages with metastases) and in 2L more broadly to achieve sales in the area of USD300m. This would make the deal with Exelixis more than rewarding and drive core earnings growth in the 13-14% CAGR range, while keeping 1L RCC, 2L HCC and other indications as free options.

- Beyond this opportunity, we now expect the new CEO David Meek, who was the architect behind the oncology franchise at Baxalta, to finalise another structuring M&A deal, with the support of the Board. We assume it will be in the same field but this time including US rights to build on Somatuline's success there because Ipsen needs a further boost to balance its business better while increasing profitability. Now competition is fierce and Ipsen must pay attention not to overpay for a target.

- If Ipsen is successful in its attempt, then endocrino-oncology would jump again from slightly more than 50% in 2015 to over two-thirds of revenues in 2020. Margins and status are likely to follow, hence our BUY rating with a slightly adjusted FV of EUR64 to factor in new FX rates.

Analyst:
Eric Le Berrigaud
33(0) 1 56 68 75 33
eleberrigaud@bryangarnier.com

Sector Analyst Team:
Mickael Chane Du
Hugo Solvet
Marion Levi (associate)

Company description

Ipsen is a global specialty-driven pharmaceutical company with total sales exceeding €1.4 billion in 2015. Ipsen's ambition is to become a leader in specialty healthcare solutions for targeted debilitating diseases. Its development strategy is supported by 3 franchises: neurology / Dysport®, endocrinology / Somatuline® and uro-oncology / Decapeptyl®. Moreover, the Group has an active policy of partnerships. At the beginning of 2016, it acquired ex-US rights of cabozantinib from Exelixis which could become a meaningful growth driver in oncology (2L renal cell carcinoma), strengthening even further an already attractive core EPS CAGR for 2016-2020. New CEO coming from the field of oncology should work in the same direction and make other deals in the field.

Income Statement (EURm)	**2013**	**2014**	**2015**	**2016e**	**2017e**	**2018e**	2019e
Revenues	1,225	1,275	1,444	1,568	1,715	1,865	2,003
Change (%)	*0.5%*	*4.1%*	*13.3%*	*8.6%*	*9.4%*	*8.7%*	*7.4%*
Adjusted EBITDA	236	311	366	408	463	544	615
EBIT	211	261	322	342	391	466	531
Change (%)	*7.4%*	*23.8%*	*23.8%*	*6.0%*	*14.2%*	*19.2%*	*14.0%*
Pre-Tax profits	201	206	237	322	353	429	498
Tax	(59.3)	(53.8)	(49.8)	(90.1)	(98.8)	(120)	(140)
Profits from associates	0.0	1.9	2.5	0.0	0.0	0.0	0.0
Net profit	142	155	190	232	254	309	359
Restated net profit	115	183	228	238	278	335	386
Change (%)	*-25.1%*	*58.3%*	*24.9%*	*4.4%*	*16.9%*	*20.4%*	*15.3%*
Cash Flow Statement (EURm)							
Operating cash flows	209	240	305	268	325	386	442
Change in working capital	(21.1)	5.3	(81.1)	(8.2)	(20.5)	(21.4)	(19.7)
Capex, net	(42.0)	(47.4)	(50.0)	(66.1)	(72.0)	(78.1)	(83.7)
Dividends	0.79	0.77	0.84	1.0	1.2	1.1	1.2
Net debt	(25.4)	(70.5)	(102)	88.1	(2.9)	(159)	(359)
Free Cash flow	146	198	174	194	233	287	338
Balance Sheet (EURm)							
Tangible fixed assets	508	556	623	835	875	915	955
Intangibles assets	456	485	505	558	558	558	558
Cash & equivalents	131	186	226	7.4	98.4	255	455
current assets	602	672	810	677	809	1,007	1,246
Total assets	1,565	1,713	1,938	2,070	2,241	2,480	2,759
L & ST Debt	374	419	450	449	469	489	508
Shareholders' funds	974	1,068	1,226	1,371	1,522	1,740	2,000
Total Liabilities	592	645	712	699	719	740	759
Capital employed	963	1,042	1,128	1,393	1,433	1,473	1,513
Financial Ratios							
Operating margin	17.19	20.43	22.33	21.81	22.77	24.97	26.50
Tax rate	29.47	26.07	20.97	28.00	28.00	28.00	28.00
Net margin	11.07	11.60	12.51	14.01	14.11	15.83	17.14
ROE (after tax)	14.57	14.47	15.52	16.90	16.69	17.77	17.95
ROCE (after tax)	15.41	18.49	22.59	17.68	19.63	22.76	25.27
Gearing	(2.61)	(6.60)	(8.29)	6.43	(0.19)	(9.16)	(17.98)
Pay out ratio	43.25	35.89	30.70	36.00	36.50	27.00	25.40
Number of shares, diluted	84.60	82.22	82.00	82.00	82.00	82.00	82.00
Data per Share (EUR)							
EPS	1.84	1.87	2.31	2.81	3.09	3.76	4.37
Restated EPS	1.85	2.22	2.78	2.90	3.40	4.09	4.71
% change	*5.8%*	*19.9%*	*25.3%*	*4.4%*	*16.9%*	*20.4%*	*15.3%*
BVPS	11.51	12.99	14.95	16.71	18.56	21.22	24.39
Operating cash flows	2.47	2.92	3.72	3.27	3.96	4.71	5.39
FCF	1.73	2.41	2.12	2.36	2.84	3.50	4.13
Net dividend	0.80	0.85	0.85	0.85	1.10	1.20	1.26

Source: Company Data; Bryan, Garnier & Co ests.

Please see the section headed "Important information" on the back page of this report.

BRYAN, GARNIER & CO

INDEPENDENT RESEARCH UPDATE

13th July 2016

Roche

Tough to perform until APHINITY delivers

Healthcare

Fair Value CHF293 (price CHF255.50) **BUY**

Bloomberg	ROG VX
Reuters	ROG.VX
12-month High / Low (CHF)	282.5 / 233.2
Market capitalisation (CHFm)	179,505
Enterprise Value (BG estimates CHFm)	191,948
Avg. 6m daily volume ('000 shares)	1,498
Free Float	91.5%
3y EPS CAGR	6.3%
Gearing (12/15)	60%
Dividend yield (12/16e)	3.46%

YE December	12/15	12/16e	12/17e	12/18e
Revenue (CHFm)	48,145	50,762	51,908	53,128
EBIT (CHFm)	13,821	17,114	18,644	19,499
Basic EPS (CHF)	10.28	13.63	15.05	15.88
Diluted EPS (CHF)	13.49	14.71	15.92	16.18
EV/Sales	4.02x	3.78x	3.64x	3.48x
EV/EBITDA	10.0x	9.4x	8.8x	8.5x
EV/EBIT	14.0x	11.2x	10.1x	9.5x
P/E	18.9x	17.4x	16.1x	15.8x
ROCE	28.1	27.9	28.7	28.6

Big pharma companies are never big enough when their main drugs are being copied. Roche's Rituxan and Herceptin (CHF14bn in sales) are exposed to that risk in 2017 and markets require plenty of innovative new drugs to offset this impact. But, in the end, it looks like one single trial (APHINITY) will make the difference between a resilient growth profile and a flattish and uninspiring one.

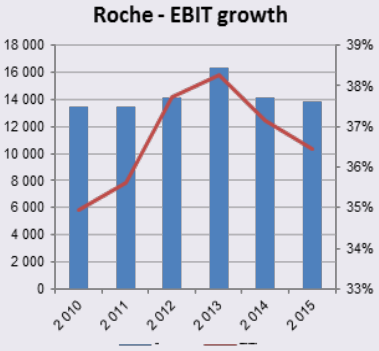
- Roche is first to recognise that APHINITY's phase III results will have a major impact on determining the growth profile of the company in the next few years. With positive results, Roche is likely to maintain top-line growth similar to what was achieved over the last five years, i.e. c.5% annual growth with, as a result, profitability very much sustained or further increased; with negative results, the most likely scenario is flat sales momentum thus translating into pressurised margins. In the first case, Roche is back with a must-have status in the universe, whereas in the second, it is dead money until it finds new opportunities to grow, including maybe a sizeable acquisition.

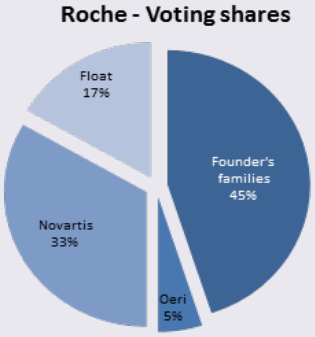
- APHINITY is assessing the value of adding Perjeta to SoC in HER2-positive adjuvant breast cancer and is expected to deliver results around the turn of the year. Like GALLIUM (and maybe GOYA too) with rituximab, APHINITY carries the power to largely reduce the impact from biosimilars on trastuzumab, adding to subcutaneous formulations of the two drugs. Its impact on the top-line is probably somewhere between CHF4bn and CHF6bn considering the size of adjuvant in the BC market and the price, which means that 80% to 90% of this amount would drop in the bottom-line.

- Sadly, all eyes are turned towards APHINITY, although Roche enters a new period of strong innovation with several other drugs which have just been launched (Tecentriq, Venclexta), are ending their regulatory phase (Ocrevus) or their clinical development (lampalizumab, ACE910). In 2022, cumulative sales from all five drugs (actually four since venetoclax is not booked in sales) are in excess of CHF8bn.

Analyst:
Eric Le Berrigaud
33(0) 1 56 68 75 33
eleberrigaud@bryangarnier.com

Sector Analyst Team:
Mickael Chane Du
Hugo Solvet
Marion Levi (associate)





Company description

Roche describes itself as the world leader in biotechnology. True is that most of its revenues in the pharmaceuticals division come from biological, including three drugs that are among the biggest in oncology worldwide: Avastin, Rituxan and Herceptin. They revolutionized their respective markets. When Roche bought Genentech's minority interests, it took full control of those assets, including a very promising R&D pipeline that looks close to delivering again. Besides pharma, Roche is also the world leader in Diagnostics which offers a balance to its portfolio of activities but also leverage to try to implement and develop companion diagnostic tests. Biosimilars clearly represent the biggest threat to Roche's business.

Income Statement (CHFm)	**2013**	**2014**	**2015**	**2016e**	**2017e**	**2018e**
Revenues	46,780	47,462	48,145	50,762	51,908	53,128
Change (%)	*2.8%*	*1.5%*	*1.4%*	*5.4%*	*2.3%*	*2.4%*
EBITDA	19,779	19,558	19,430	20,345	21,444	21,699
EBIT	16,376	14,090	13,821	17,114	18,644	19,499
Change (%)	*15.9%*	*-14.0%*	*-1.9%*	*23.8%*	*8.9%*	*4.6%*
Core EBIT	17,904	17,636	17,542	18,457	19,744	19,999
Financial results	(1,699)	(1,575)	(1,834)	(1,183)	(930)	(825)
Pre-Tax profit	14,677	12,515	11,987	15,931	17,713	18,674
Exceptionals	0.0	0.0	0.0	0.0	0.0	0.0
Tax	(3,304)	(2,980)	(2,931)	(3,983)	(4,517)	(4,762)
Profits from associates	0.0	0.0	0.0	0.0	0.0	0.0
Minority interests	209	203	193	200	220	220
Net profit	11,164	9,332	8,863	11,748	12,976	13,692
Core Net Income	12,317	12,329	11,626	12,677	13,722	13,947
Change (%)	*5.8%*	*0.1%*	*-5.7%*	*9.0%*	*8.2%*	*1.6%*
Cash flow Statement (CHFm)						
Operating Cash flows	17,458	16,885	16,542	15,614	17,193	16,996
Change in working capital	209	258	431	1,536	1,056	370
Capex, net	2,386	2,902	3,423	3,200	2,800	2,800
Financial investments, net	401	368	636	0.0	0.0	0.0
Dividends	7,661	7,694	7,921	7,055	7,693	8,327
Net debt	6,708	14,011	14,080	12,443	9,316	5,421
Free Cash flow	13,321	12,964	11,783	9,876	11,750	13,047
Balance Sheet (CHFm)						
Shareholders' funds	21,241	21,558	23,300	28,193	33,696	39,281
+Provisions	3,245	4,243	4,636	4,636	4,636	4,636
+Net debt	6,708	14,011	14,080	12,443	9,316	5,421
=Invested Capital	31,194	39,812	42,016	45,272	47,648	49,338
Fixed assets	27,660	41,007	44,375	45,295	45,815	46,335
+ Working Capital	5,837	5,135	3,826	5,362	6,418	6,788
+ Other	(2,303)	(6,330)	(6,185)	(5,385)	(4,585)	(3,785)
=Capital Employed	31,194	39,812	42,016	45,272	47,648	49,338
Financial Ratios						
Operating margin	35.01	29.69	28.71	33.71	35.92	36.70
Core operating margin	38.27	37.16	36.44	36.36	38.04	37.64
Tax rate	22.51	23.81	24.45	25.00	25.50	25.50
Net margin	26.33	25.98	24.15	24.97	26.43	26.25
ROE (after tax)	66.08	48.00	43.70	50.37	45.83	40.70
ROCE (after tax)	42.44	29.75	28.05	27.85	28.69	28.56
Gearing	31.58	64.99	60.43	44.13	27.65	13.80
Pay out ratio	54.65	56.00	60.06	60.06	60.06	60.06
Number of shares, diluted	863	863	862	862	862	862
Per share data (CHF)						
EPS	12.94	10.81	10.28	13.63	15.05	15.88
Restated EPS	12.94	10.81	10.28	13.63	15.05	15.88
Core EPS	14.27	14.29	13.49	14.71	15.92	16.18
change (%)	*4.8%*	*0.1%*	*-5.6%*	*9.0%*	*8.2%*	*1.6%*
Goodwill	0.0	0.0	0.0	1.00	2.00	3.00
BV	22.36	22.70	24.34	29.78	35.91	42.13
Operating cash flow	20.23	19.57	19.19	18.11	19.95	19.72
Free Cash flow	15.44	15.02	13.67	11.46	13.63	15.14
Net dividend	7.80	8.00	8.10	8.83	9.56	9.72

Source: Company Data; Bryan, Garnier & Co ests.

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BRYAN, GARNIER & CO

London
Beaufort House
15 St. Botolph Street
London EC3A 7BB
Tel: +44 (0) 207 332 2500
Fax: +44 (0) 207 332 2559
Authorised and regulated by the Financial Conduct Authority (FCA)

Paris
26 Avenue des Champs Elysées
75008 Paris
Tel: +33 (0) 1 56 68 75 00
Fax: +33 (0) 1 56 68 75 01
Regulated by the Financial Conduct Authority (FCA) and the Autorité de Contrôle prudential et de resolution (ACPR)

New York
750 Lexington Avenue
New York, NY 10022
Tel: +1 (0) 212 337 7000
Fax: +1 (0) 212 337 7002
FINRA and SIPC member

Munich
Widenmayerstrasse 29
80538 Munich
Germany
+49 89 2422 62 11

New Delhi
The Imperial Hotel Janpath
New Delhi 110 001
Tel +91 11 4132 6062
+91 98 1111 5119
Fax +91 11 2621 9062

Geneva
rue de Grenus 7
CP 2113
Genève 1, CH 1211
Tel +4122 731 3263
Fax+4122731 3243
Regulated by the FINMA