BRYAN, GARNIER & CO

INDEPENDENT RESEARCH

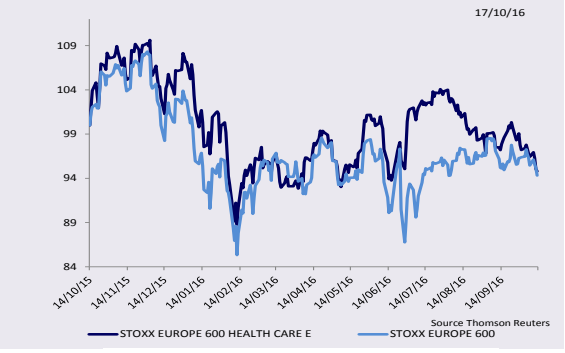
Healthcare

19th October 2016

Back from ESMO 2016: What's hot in oncology

Healthcare

ASTRAZENECA		**BUY**	**FV 5220p**
Bloomberg	AZN LN	Reuters	AZN.L
Price	5002p	High/Low	5220/3774
Market cap.	GBP63,276m	Enterprise Val	GBP75,672m
PE (2016e)	15.5x	EV/EBIT (2016e)	14.1x
GENMAB		**BUY**	**FV DKK1600**
Bloomberg	GEN DC	Reuters	GEN.CO
Price	DKK1137	High/Low	1266/634
Market Cap.	DKK68,503m	Enterprise Val	DKK63,728m
PE (2016e)	NS	EV/EBIT (2016e)	NS
INNATE PHARMA		**BUY**	**FV EUR18**
Bloomberg	IPH FP	Reuters	IPH.PA
Price	EUR10,72	High/Low	14,53/9,54
Market Cap.	EUR578m	Enterprise Val	EUR377m
PE (2016e)	18.7x	EV/EBIT (2016e)	14.4x
NOVARTIS		**NEUTRAL**	**FV CHF87**
Bloomberg	NOVN VX	Reuters	NOVN.VX
Price	CHF75,15	High/Low	90,55/68,5
Market Cap.	CHF197,428m	Enterprise Val	CHF190,389m
PE (2016e)	15.8x	EV/EBIT (2016e)	15.8x
ROCHE HOLDING		**BUY**	**FV CHF293**
Bloomberg	ROG VX	Reuters	ROG.VX
Price	CHF233,6	High/Low	279,3/232,7
Market Cap.	CHF164,119m	Enterprise Val	CHF176,784m
PE (2016e)	14.8x	EV/EBIT (2016e)	9.0x
IPSEN		**BUY**	**FV EUR72 vs. 67**
Bloomberg	IPN FP	Reuters	IPN.PA
Price	EUR63,16	High/Low	63,62/47,1
Market Cap.	EUR5,259m	Enterprise Val	EUR5,280m
PE (2016e)	20.5x	EV/EBIT (2016e)	14.7x



Medical congresses in oncology are increasingly being infiltrated by immuno-oncology which is taking a leading audience as illustrated by the crowd trying to attend the Presidential Session on Sunday, 9 October at ESMO. This document is our feedback from the congress that addresses our selection of highlights in IO and beyond.

- It is not unreasonable to start with anything other than the three presentations which took place on that Sunday in the too-small Copenhagen auditorium: KEYNOTE 024 (pembro in high-PDL1+ 1L NSCLC pts vs platinum), CHECKMATE 026 (nivo in PDL1+ 1L NSCLC pts vs BSC) and OAK (atezo in unselected 2L/3L NSCLC pts vs. docetaxel). The results provoked a storm for nivo because the degree of failure was unexpected and behind it possibly imbalances in the baseline characteristics of the trial, though some suggested an inferior drug. So 1L in NSCLC remains largely open for IO, likely through combinations.
- We were expecting two other classes to be under the spotlight: this was very much the case for CDK4-6 inhibitors and MONALEESA-2 phase III data, mainly read as confirmatory results for the class. This is likely to become SoC in ER+ BC with Pfizer leading the pack with first-in-class Ibrance. Differentiating factors for LEE011 (Novartis) do not seem to be major ones. However, PARP inhibitors, although supported by class 1 results from NOVA in ovarian cancer, are more likely to be on the front scene next year as more data become available, including in breast cancer.
- Interesting battles between IO and targeted therapies are taking place in melanoma (with an apparent debate between physicians and payers) and in RCC where the best-in-class results of cabozantinib were discussed in light of the parallelled results of nivo and upcoming ones with other IO drugs. The probability of being able to file Cabo in 1L based on phase II data has increased and the drug could get the indication on-label by YE 2017.

In satellite meetings, pricing was a point of discussion and we would caution before extrapolating efficacy results too quickly into sales because some drug benefits will be discussed in relative terms.

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1. IO is the magic word

1.1. From surveillance to "prison break"

This section is a copy of our introductory comment to the report issued after our BG Oncology Day in June because it is worth keeping in mind what we are talking about when we use the word IO.

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. 1: 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

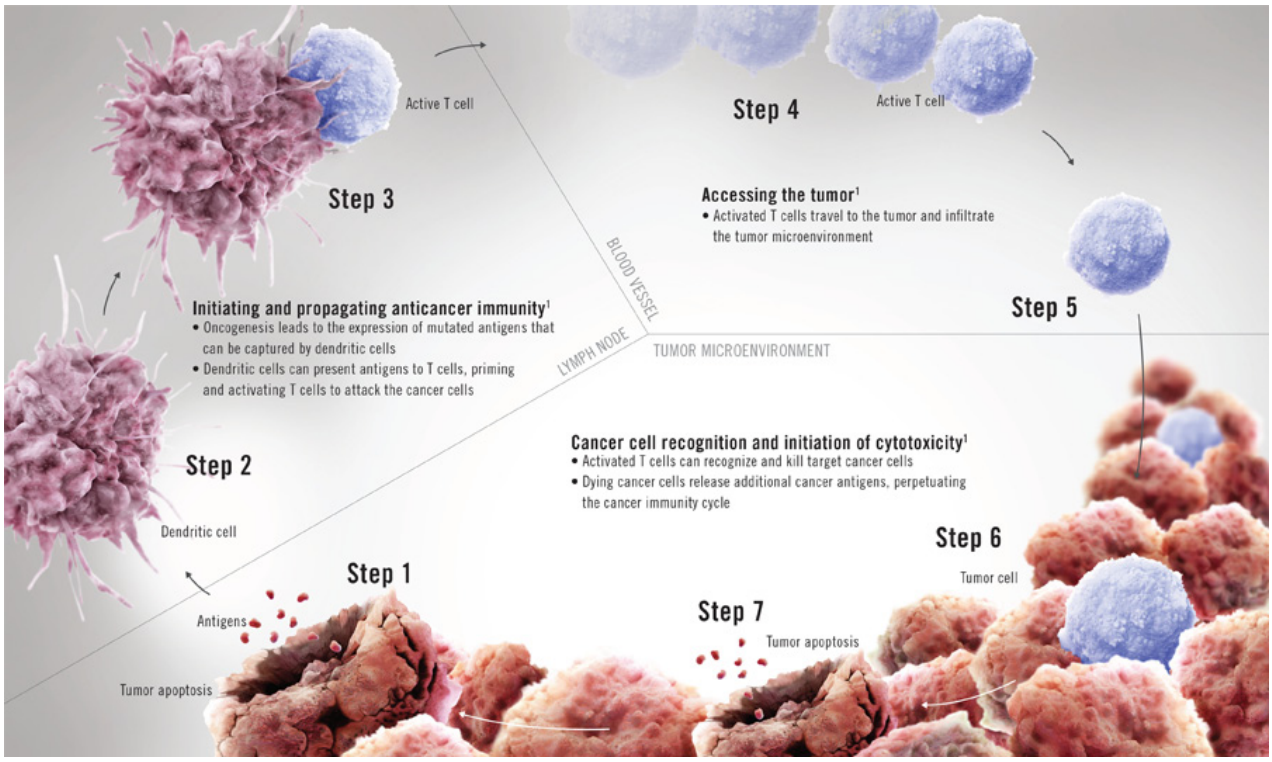
Now turning to the immune response against cancers, we can roughly divide it into three big steps ultimately leading to the death of cancer cells:

- **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. 2: 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.

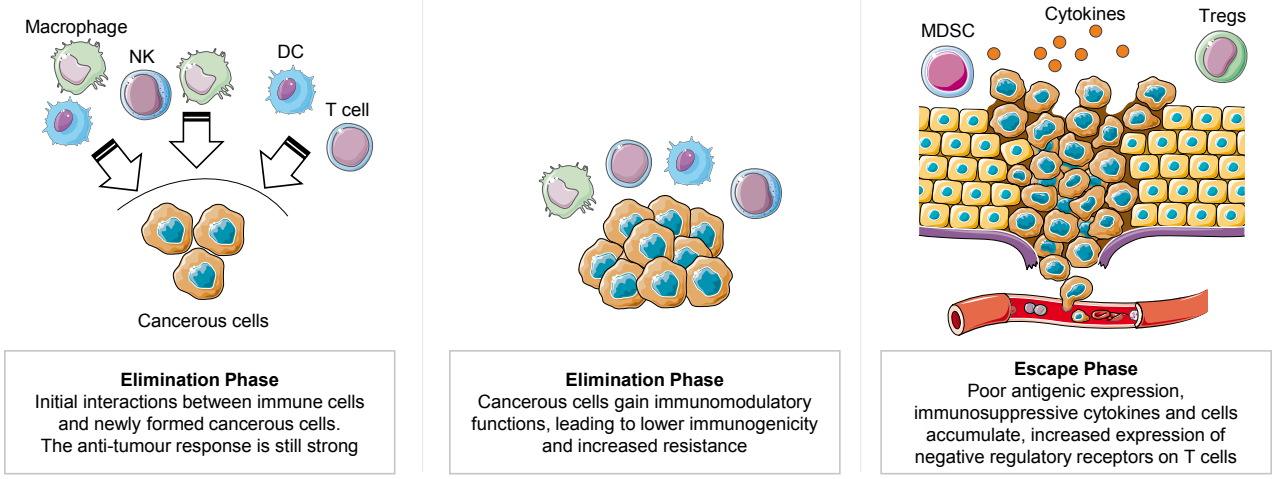
- **The three Es of cancer immuno-editing**

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

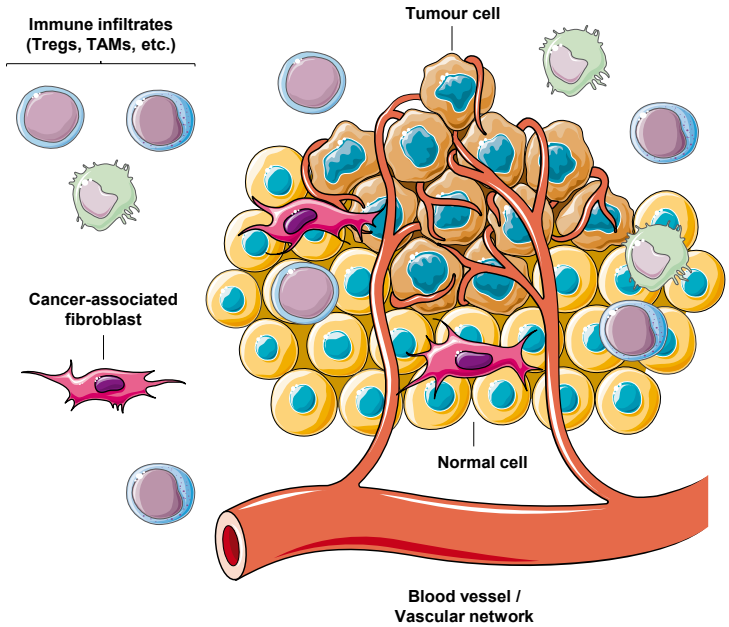


Source: Adapted from Kim et al., *2007; Bryan, Garnier & Co. ests.*

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. 4: The TME: a quite complex ecology



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

1.2. Disruptive IO fully reflected at ESMO

Sunday, 9 October, clearly put immuno-oncology drugs at the forefront of the ESMO congress in Copenhagen and a full Presidential Session was dedicated to the key publications in this field.

Anecdotally, the *Daily Reporter,* which is the internal newspaper of the ESMO congress released every day, put on its front page on that day, i.e. took as the key message from the previous day's presentations, the results with ipilimumab in adjuvant melanoma. In our view, this was very illustrative of the central position already occupied by IO at ESMO while we are still at the beginning of its journey. It is also objective to say that toxicity (15 out of 18 patients stopped treatment before the end of the study in OpACIN for instance) does not look like an issue. However, in less prestigious satellites, the question of cost was raised and already today is creating big inequalities across regions and countries: "high cost is a barrier" clearly stated an Italian oncologist that was talking about IO/IO combinations in lung cancer. Another person, who works in France, highlighted that IO was not permitted in V600 mutated metastatic melanoma cancer because targeted therapies are available and are preferred options. One key question therefore remains about IO: who should one give each drug to, how and how long? Some speakers suggested that, in real life, they might decide to give some IO drugs for less long than showed in clinical trials because they act as gate-openers and their effect usually goes beyond treatment interruption. To be continued.

IO had prime position at ESMO

So, with that said, there were several interesting presentations that, overall, suggested the marked influence of PD-1 and PD-L1 agents in many solid tumour types. It is worth saying that nivolumab and pembro were the more popular drugs discussed, reflecting their advance in several settings. However, it is also fair to say that, at least at the time of the conclusion of many discussions, hopes about combinations reaching an even greater level of response and efficacy were often formulated, for instance in TNBC or in kidney cancer, and also by discussants in the Presidential Session.

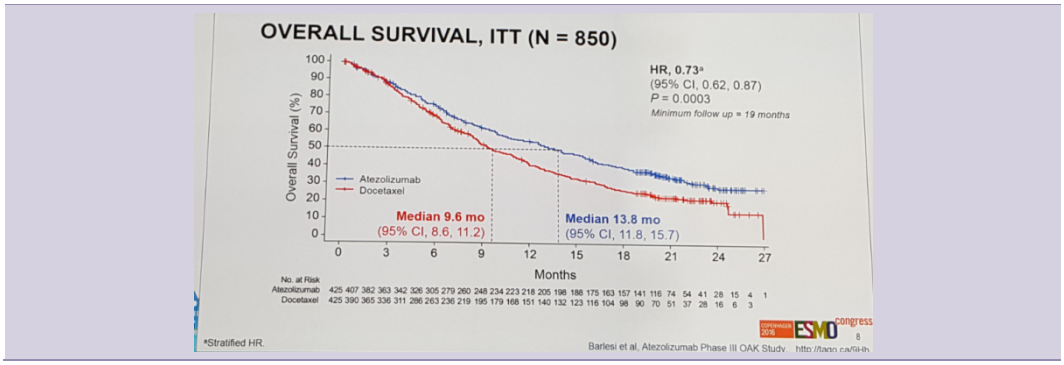
1.2.1. Three trials highlighted in the Presidential Session

So let's say a few words about each of the three key presentations that took place during the Presidential Session taking the angle of learning for the European players in our coverage.

1.2.1.1. OAK highly supportive of atezo in 2L/3L NSCLC

From this perspective, of course, OAK first phase III data were the most significant and we would say also the less-debated results (based on overall survival) as atezolizumab clearly showed superiority over docetaxel across the board, i.e. irrespectively of patient characteristics and subgroup analysis and notably between squamous and non-squamous NSCLC, with or without CNS metastases, whatever the smoking status and between PD-L1 positive and negative.

Fig. 5: OS results from first OAK phase III data analysis (1)



Source: Roche, ESMO 2016

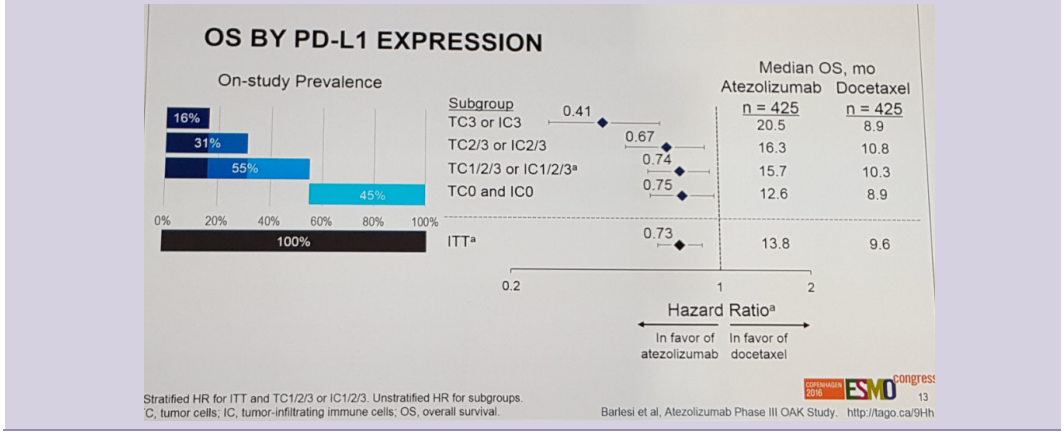
Curves separated early and in the end atezolizumab demonstrated a median OS of 13.8 months vs 9.6 months for docetaxel (HR=0.73, p=0.0003) and this came with an overall good safety profile with 15% grade 3-4 adverse events related to the treatment vs 43% for the taxane. We would note that, like other PD-1 drugs previously, PFS did not show statistical difference between arms.

Benefit across all subgroups

As said and as illustrated in Fig.4 below, the benefit was seen across all subgroups irrespective of the level of PD-L1 expression. It may come as a surprise to see how well patients with TC0 and IC0 responded with monotherapy PD-L1 but Roche was firm in saying that this did not come from the assay used and that 0.0 were true 0.0. So, in a context when, in real life, patients are unlikely to be tested several times for the PD-L1 status of their tumour across the treatment lines, having a drug that works irrespective of the PD-L1 level of expression in 2L/3L is a key advantage.

When looking at the other end of the spectrum, i.e. the highest PD-L1 expressers, this is however where atezo delivered the strongest efficacy results with a median OS of 20.5 months and an HR of 0.41. And here, it is interesting to make a comparison with what Merck reported with pembro earlier this year in *The Lancet* from the KEYNOTE-010 trial. Although stratification based on PD-L1 expression is not identical, median overall survival was 14.9 and 17.3 months in the 2mg/kg and 10mg/kg arms respectively in high expressers compared to 8.2 months in the docetaxel arm. In OAK, the docetaxel arm reported a median survival of 8.9 months, which is close, but atezo did better.

Fig. 6: OS results from first OAK phase III data analysis (2)



Source: Roche, ESMO 2016

In conclusion, we would say that atezolizumab appears to be at least as effective as PD-1 drugs already approved in the same setting of 2L/3L NSCLC with maybe a clearer advantage in terms of persistence of efficacy (interaction with B7.1?), across various populations (including 0.0 and high expressers), obtained from one large trial with 1,225 patients and with a Q3w treatment interval scheme (vs Q2W for nivo).

As a reminder, Roche is expecting the FDA to act on Tecentriq's first BLA in advanced PD-L1 positive NSCLC by the end of the week and, with pembro's success in 1L, is expecting to get a significant share of the 2L/3L setting with atezo monotherapy while continuing to explore combinations to compete in 1L.

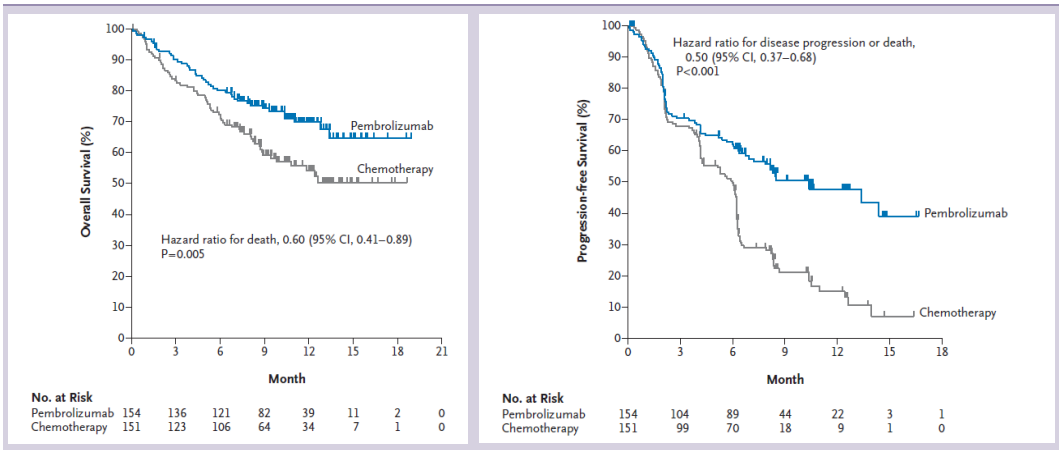
1.2.1.2. KEYNOTE-024: in the end a fairly small opportunity?

Good results but in the end only about 10% of 1L NSCLC ?

So, precisely, let's now move to KEYNOTE-024 which is the study that investigated pembrolizumab 200mg every three weeks against platinum-based therapies in 1L NSCLC with PD-L1 expression of 50% or more. Needless to say that the results are outstanding with HR of 0.50 for median PFS and 0.60 for median OS. The overall response rate also clearly favoured pembro (45% vs 28%) with six complete responders and with the exception of people that have never smoked (with no difference based on a small subgroup of only 24 patients), all subgroups benefited from pembro.

As with atezo, safety was also in favour of the PD-1, notably grade 3-5 adverse events with an incidence of 26.6% (vs 53.3%). Treatment-related AEs occurred at a similar rate in both arms. Less events led to treatment discontinuation in the pembro arm than in the CT arm (7.1% vs 10.7%).

Fig. 7: KEYNOTE-024: median OS (left) and PFS survival (right) curves

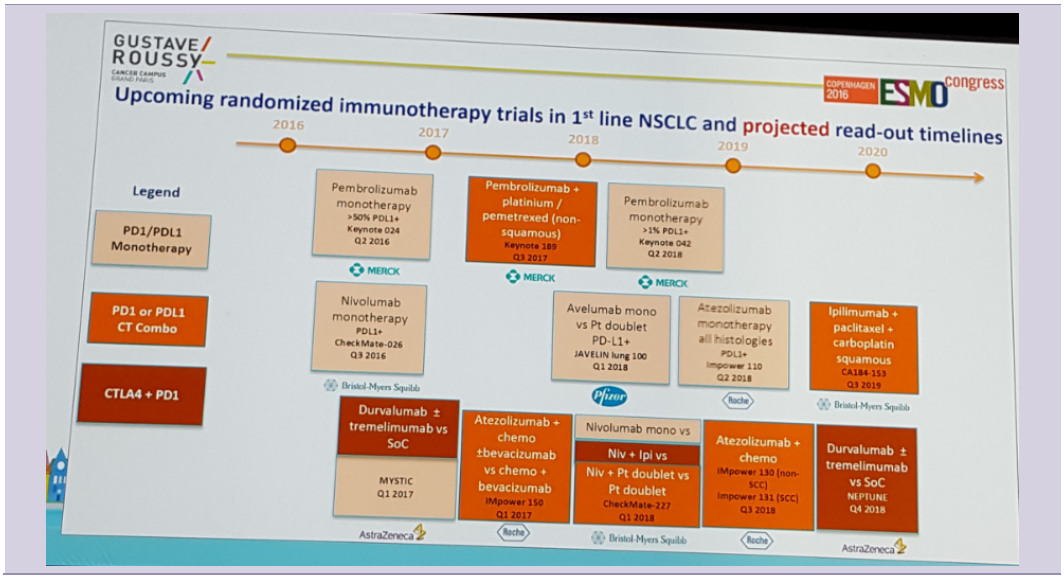


Source: NEJM

However, what was very interestingly raised by discussant Jean-Charles Soria from IGR, who noted the unprecedented ORR of 45% for a PD-1 in monotherapy (vs 28%, p=0.0011) and the outstanding results in squamous cell lines (HR=0.35), is the limited population addressed by the study. Not only PD-L1 high expressers do represent only a quarter of NSCLC patients (23-28% as reported in the *NEJM* publication) but once the exclusion criteria are considered (no ALK or EGFR mutation, no brain metastasis, no active autoimmune disease, no ongoing immunosuppressive therapy, no glucocorticoid therapies, etc…), it is only 10-15%. This is how Merck came from 1,934 patients screened down to 305 randomised patients.

So, on one hand, the results are clearly suggestive of a benefit of using IO in 1L NSCLC, maybe even vs 2L/3L, but so far the evidence is data-based in only a small subset of the total population. This leaves room for new agents and combinations to take a greater part of the 1L NSCLC pie. CHECKMATE-227 and MYSTIC have been mentioned more particularly with respectively nivolumab and durvalumab, but the list is fairly long (see Fig.8).

Fig. 8: Phase III trials involving IO drugs in 1L NSCLC



Source: ESMO 2016, slide presented by discussant J.C.Soria (IGR, Villejuif)

1.2.1.3. CHECKMATE-026: when iconic Opdivo is seriously hit

Serious failure of Odivo in 1L NSCLC trial

Lastly, we conclude with the CHECKMATE-026 trial which was a failure for BMS in demonstrating benefit for nivolumab in 1L PD-L1 positive NSCLC vs doublet chemotherapy.

It was a complete failure as all parameters favoured the CT arm which includes median PFS (HR=1.15), median OS (HR=1.02) and ORR (26.1% vs 33.5%). The primary endpoint was the measure of the median PFS in patients with untreated NSCLC and PD-L1 expression of 5% or more, and Opdivo achieved 4.2 months compared to 5.9 months with doublet chemotherapy (usually pemetrexed-based).

Some imbalances between groups (more female and more PD-L1 high expressers in the CT arm) may have participated in the failure (usually females do respond better to CT and they were 45% vs 32%) but the magnitude of the failure suggests further investigation to understand what may have happened. The level of PD-L1 expression in the inclusion criteria of the study was much higher in KEYNOTE-024 than in CHECKMATE-026 but post-hoc subgroup analysis could have made it possible to offer a second reading of the results, including by balancing males with females. If it has not been done (or not been shared), it is probably because it is likely to be worse than just a trial design issue. Actually, beyond the design and the conduct of the trial, the issue could be that nivo is a perfectible drug in this specific setting compared to others.

The good thing is that it leaves a very significant part of the NSCLC market still open in 1L to new options. As illustrated above, several combinations are currently being tested that will start reporting results in 2017 or in 2018 if PFS proves insufficient.

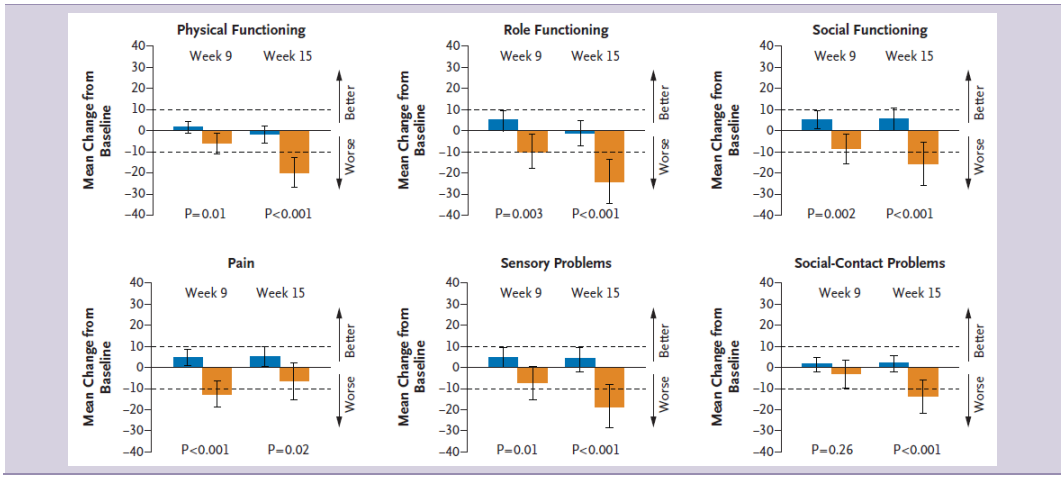
1.2.2. Impressive results across the board

The three key presentations detailed in the earlier part of this note were all NSCLC-related but, of course, the influence of IO goes far beyond lung cancer and this has been well captured and well disseminated at ESMO.

We have said a bit about melanoma already, where IO and IO/IO combination nivo/ipi have already established themselves as references, despite competition in the V600 mutated market segment, but it is going well beyond this indication and we would like to report here some additional results and comments from various other presentations:

- Presentation of CHECKMATE-141 detailed results also took place during the Presidential session and mainly focused on the QoL (quality of life) questionnaire. It is worth keeping in mind that nivo brought the median OS up from 5.1 months with physicians' choice (methotrexate, docetaxel, Erbitux) to 7.5 months in 2L SCCHN (squamous-cell carcinoma of the head and neck) after a platinum-based 1L of therapy. Put simply, nivo came out better on all criteria (fatigue, loss of appetite, pain, sensory events, social contact, etc…), with no difference between PD-L1 positive and negative patients. It is also worth noting that median time to deterioration (mTTD) was three times higher in the nivo group.

Fig. 9: QoL and symptom burden as reported in CHECKMATE-141 phase III trial



Source: ESMO 2016, NEJM.

Two main take-aways here: (i) first, IO has a key role to play in SCCHN in advanced lines because, as stressed by the discussant, after standard 1L made of 5-FU/Erbitux with either carboplatin or cisplatin, there are limited working options. Ongoing phase III trials using other agents like KEYNOTE-040 (with pembro) and EAGLE (with durva) should confirm this new standard of care in 2L SCCHN. To note is that the three compounds are also currently being investigated in 1L (CHECKMATE-651, KEYNOTE-048, KESTREL); and (ii) if IO is popular among oncologists, this is also because they are usually safe options, in particular PD-1/PD-L1 targeting agents.

- Presentation of KEYNOTE-021 cohort G data was also interesting in that it is a first insight into the synergistic effect that can be expected from the combination of a PD-1 with CT (in this case carboplatin/pemetrexed) in 1L NSCLC. The trial was a phase II in non-squamous NSCLC (123pts allocated).

The results were very good, to say the least, including an outstanding ORR of 55%, with no difference across subgroups which comprises a relatively homogeneous behaviour across the various levels of PD-L1 expression This would be confirmatory of a meaningful difference compared to IO drugs when used in monotherapy. Median PFS was 13 months compared to 8.9 months (HR=0.53, p=0.0102) whereas it was too early to detect a potential difference in median OS, while 32% of patients in the comparative arm crossed over to receive pembro thus reducing the power of the trial to detect differences.

Safety-wise, which is often a key question when combining IO with chemotherapy, there was a slight imbalance against the active arm when considering grade 3-4 side effects but with no impact on drug discontinuation rates.

The results are encouraging for the IO/CT combinations developed in 1L NSCLC based on the response rate across all groups with an acceptable safety profile. Merck has a phase III ongoing with the same design (KEYNOTE-189), which should report sometime between the very end of 2017 and early 2018. This is obviously good news also for Roche which is also expecting results sometime in 2017 in squamous and non-squamous NSCLC.

- Presentation of CHECKMATE-040 data also resulted in very encouraging efficacy for nivolumab in advanced HCC after 1L with TKi. 82% of the patients included in the trial had received sorafenib in 1L and the majority were HBV and/or HCV infected. The objective response rate was 15%, and 50% had stable disease, and this was achieved across all subgroups although it was higher in PD-L1 positive patients. When patients responded, the median duration of the response was 17 months and median OS was 14.3 months, which compares favourably to recently-published RESORCE phase III results using regorafenib as the active drug, which achieved a median OS of 10.6 months (HR=0.62).

  In HCC, the question is no longer if PD-1/PD-L1 are going to be used but how and when. BMS has already initiated a phase III trial in 1L HCC comparative to sorafenib (CHECKMATE-459) whose first results are expected by the end of H1 2017. Should IO drugs move into 1L HCC, the question about the best drug to use in 2L would be an open one and the choice between sorafenib and regorafenib not easy to make. Unless a new player can do even better like Exelixis/Ipsen's cabozantinib whose results in 2L HCC are expected in 2017 too.

- A last word to report on what we heard in a session dedicated to TNBC which are representing a very heterogeneous group of tumours defined by what they are/have not rather than by what they are/have. With the exception of mBRCA TNBC (where platinum-based regimens work well), there is no guidelines about the best therapy to use but high hopes to see PARP inhibitors, AKT inhibitors or PI3K inhibitors working in some subgroups of TNBC. However, it was also stressed that some TNBC have more mutations than others which could increase the chances of seeing IO drugs being effective. Preliminary data in small phase I/II trials have shown interesting 18-19% ORR with either pembro or nivo and it has been suggested that combinations with targeted therapies might be even more effective while also combining early response with durable response.

2. Is there anything outside IO to report?

If IO is obviously a revolution in the field of oncology, although it is still in its very early phase, then it would be a mistake not to look beyond IO because as, we already stated in previous reports, including after our BG Oncology Day in July 2016, the emergence and growing importance of IO does not mean that other approaches are dead. We do not see CT-free regimens as standards in the majority of solid tumour protocols, at least over the next few years. The synergistic effect of IO with either CT or some targeted therapies more than balances the drawbacks of using them in combination. Moreover, they are well-known and, as such, physicians have learnt how to use them, which is not the case with IO drugs (titration, sequence, maintenance, etc…).

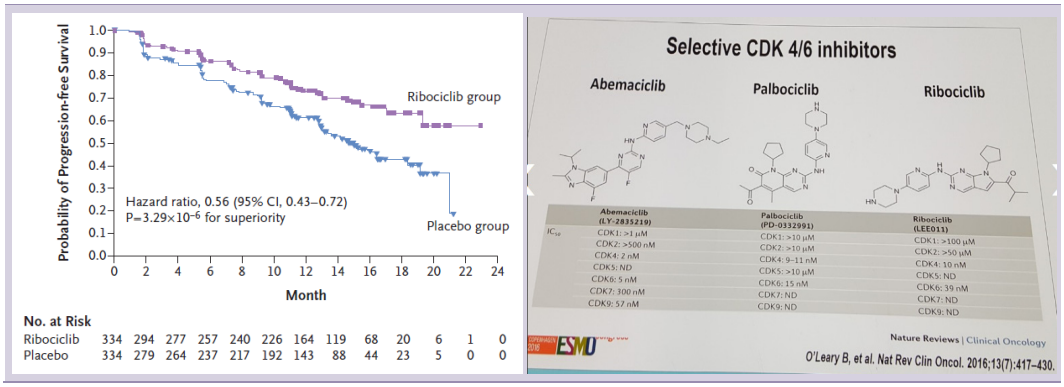
With this in mind, we found two non-IO presentations particularly interesting to report and a third that will deserve further investigation and that should be a class of focus next year.

LEE011 confirms central role to be played by CDK4/6 inhibitors

2.1. CDK4/6 inhibitors: a major role in ER+ BC

If we had had to go home with only one major idea from non-IO presentations, it would be the growing evidence of the strong influence of CDK4-6 inhibitors in ER-positive breast cancer. Be it in a presentation about biomarker analysis in the PALOMA-2 study comparing palbociclib/letrozole to letrozole or in the big presentation during the Presidential Session on Saturday of the MONALEESA-2 phase III results, the common conclusion is that CDK4-6 inhibitors work irrespective of the subgroups. Different hypotheses have been tested, including p16 or Ki-67 status as predictive markers, but they failed to establish a difference. Finally, as he concluded that CDK4-6 inhibitors would probably be game-changing for the treatment of ER+ BC, invited discussant S. Johnston simply questioned how these drugs should be used. And maybe the only relevant question left at this stage is to know if endocrine sensitivity vs endocrine naïve vs endocrine resistant tumours make a difference or if they deserve being used across the board. But what is true is that the results are impressive when they are compared to aromatase inhibitors that had already been a significant advance in the treatment of ER+ BC. Median PFS jumped from 14.5 to 24.8 months in the PALOMA-2 study whereas it is not yet reached in MONALEESA-2 by the active arm vs 14.7 months for the comparative arm (HR=0.556).

Fig. 10: PFS results in MONALEESA-2 phase III trial (left) – Comparison of CDK4-6 inhibitors (right)



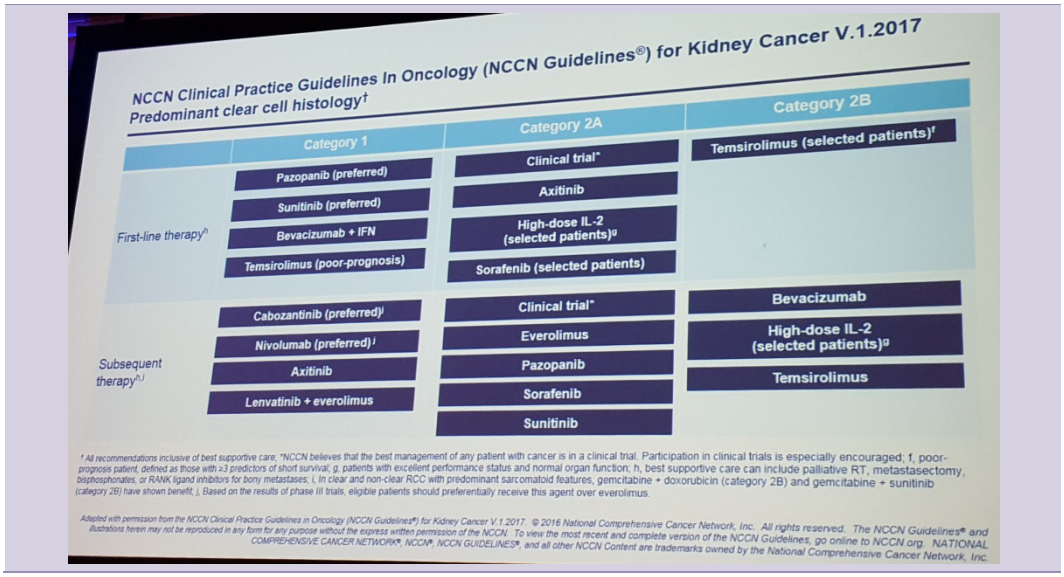
Source : NEJM(left), picture from ESMO 2016 (right)

In both cases, it has been highlighted how quickly the two curves were separating (especially in contrast with fulvestrant which also presented solid data in FALCON but with late benefit and almost exclusively when there is no visceral disease). And safety is globally very good with limited numbers of grade 3 side-effects (mostly neutropenias and leukopenias, including five cases of febrile neutropenias), which are asymptomatic and usually manageable with treatment interruption. We would note however that there were four patients who met criteria of Hy's Law in the combination arm. As a second-to-market agent, this is something regulators might pay more attention to. That said, presenters mainly commented on the results as being meaningful confirmatory results of palbociclib, now forming the evidence of the central role to be played by CDK4-6 inhibitors in 1L ER+ breast cancer. Pfizer's drug is likely to take the lion's share of this market (all the more so if it succeeds in the adjuvant setting too) but LEE011 will nevertheless be a multi-blockbuster drug even with a 20% share (or more).

2.2. Cabozantinib: Too late for a TKi?

Results from the two trials METEOR (phase III in 2L RCC, already presented at ASCO) and CABOSUN (phase II in 1L RCC, presented for the first time) are strongly supporting the use of cabozantinib in RCC. But of course, the competition that is very likely to take place against IO drugs in this setting makes it very difficult to say for sure that cabozantinib will have an easy game. So far, cabozantinib and nivolumab are treated equally, as reflected in the most recent and updated guidelines (see Fig. 11), with preferred status.

Fig. 11: Updated NCCN guidelines in mRCC



Source : NCCN, picture from presentation at ESMO 2016

Now, if it does not help claim superiority for either of nivolumab or cabozantinib in RCC, CABOSUN maybe says that cabozantinib is the best available tyrosine kinase inhibitor compared to the older ones, none of which ever achieved positive OS, PFS or ORR in trials.

CABOSUN recruited 150 patients with clear-cell RCC naïve to therapy and having a poor or intermediate risk, i.e. having the poorer prognosis (in 2L they will have between 5.4 and 16.6 months median survival rate), including 37% with bone metastases. This population represents between 70% and 75% of the overall RCC population.

The primary endpoint was the median PFS and it was expanded from 5.6 to 8.2 months (HR=0.69, p=0.012), with benefit across all subgroups, although it is fair to say that those with bone metastases benefited the most. The difference in ORR was also outstanding at 46% vs 18% (when assessed by the investigator). Dose reductions occurred in 58% and 49% respectively in the cabo arm and the sunitinib arm, grade 3-4 side effects appeared very comparable across the two arms (65% vs 68%) and grade 5 AEs infrequent (5% vs 4%). So these are very strong and consistent data in a setting where nothing has emerged for a long time.

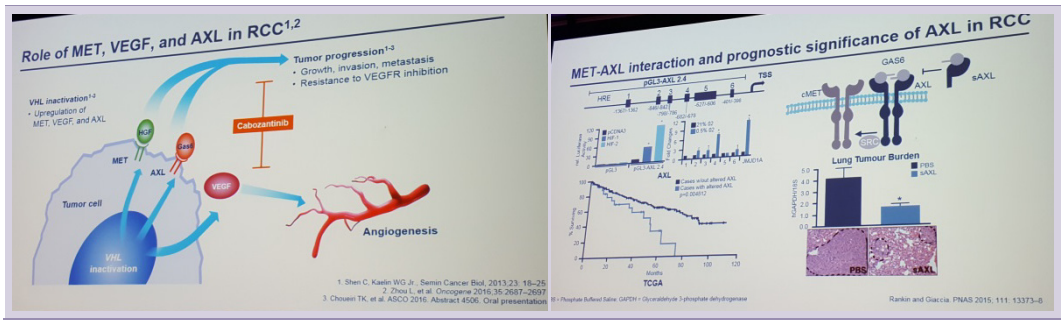
And actually everything carried on very well until the last part of the discussant Prof. Escudier's speech when he stated that, based on the absence of median OS benefit (HR=0.80 with 30.3 months vs 21.8 but p=NS), he would not be comfortable prescribing the drug in 1L until confirmatory data from a phase III trial. This came as a very unexpected comment from one of the most respected specialists in Europe. Exactly at that time, Exelixis's share price collapsed in the US.

Asked similarly about what they would do, three US specialists invited by Ipsen and Exelixis went against this conclusion. They showed that sunitinib did very much as expected in this trial and like in previous ones and, despite a limited follow-up, OS benefit is likely to be confirmed later. In any case, with a clear benefit on mPFS and ORR, cabozantinib proves superior to sunitinib and time will tell about nivolumab and others in this setting. In PC trials, it has been showed that cabozantinib might well prepare the milieu or make the environment permissive for a better effect of an IO drug. So cabo first makes a lot of sense, even though safety can be called into question. But patients might prefer an oral drug. Lastly, some preliminary phase I data, mostly in bladder cancers, showed interesting efficacy and safety data in heavily pre-treated patients that are reassuring for the safety of the combination and convinced Exelixis to start a phase II trial in bladder cancer. Cabo+Nivo vs Cabo then Nivo looks like an interesting phase III to perform.

Cabo to play a key role in mRCC although positioning is yet unclear

So, in the end, our belief is that cabozantinib, whatever its precise setting, is here to play a key role in RCC. Because of its mode of action which not only involves the VEGFR pathway but also MET and AXL, it is now the TKi of choice and it is a bit too early to say how IO will navigate around. Moreover, 5-10% of patients who have immune diseases are not eligible to IO and those with bone mets are also clear candidates for cabo. So, the size of the market opportunity remains to be carefully measured but CABOSUN data are clearly helpful to give cabozantinib a central place in RCC.

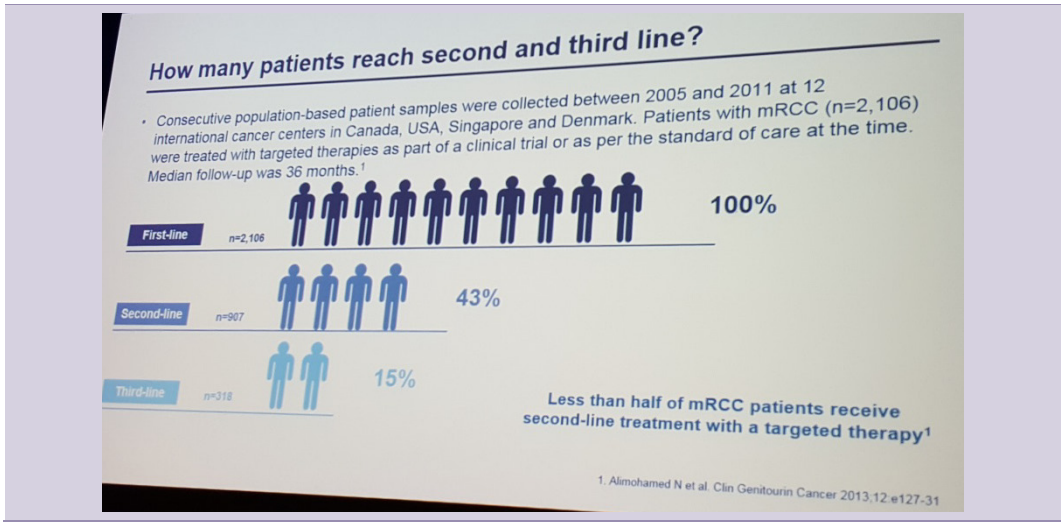
Fig. 12: Cabozantinib: a TKi with a unique mode of action against MET and AXL



Source: pictures from presentations at ESMO 2016

What can now happen with 1L RCC? Well, the optimism to be able to file on phase II data has clearly increased at Exelixis and Ipsen. The ability to file by the end of H1 2017 and to have a variation procedure in Europe making it possible to get an approval by year-end 2017 is real. This would be a major upside to our scenario and, although the median duration of treatment based on mPFS might not be massively increased by getting in 1L, it is said that more than half of the patients are lost between 1L and 2L, thus reducing dramatically the target population (see Fig. 13).

Fig. 13: Only 4 out of 10 patients would reach second line in mRCC



Source: picture from ESMO 2016

Our new PS is EUR450m for cabo in Ipsen's territories

In conclusion, we keep 2L mRCC as the market cabozantinib will mainly address and target, until we know if CABOSUN can be accepted for filing or if confirmatory phase III is needed. We will use incidence instead of prevalence to build our sales model as this is how we expect annual sales to be generated (so 84,400 patients in Europe according to 2012 data, 10% more for the rest of the world). We have assumed that 40% of them would take 2L of treatment, we have kept 12% as the discontinuation rate for adverse events and we have attributed progressive market share to cabozantinib of up to 30% (10% in 2019, 20% in 2021 and 30% in 2025). We have set an average net price of EUR60,000 per annum but have considered only 75% of that to reflect the duration of treatment based on the median PFS. Our PS moves from EUR300m to EUR450m in 2025.

Fig. 14: Cabozantinib sales model for Ipsen's territories

	2016e	2017e	2018e	2019e	2020e	2021e	2022e	2023e	2024e	2025e	2026e	2027e
Incidence Europe RCC	84,400	84,400	84,400	84,400	84,400	84,400	84,400	84,400	84,400	84,400	84,400	84,400
10% extra incidence for ROW	8,440	8,440	8,440	8,440	8,440	8,440	8,440	8,440	8,440	8,440	8,440	8,440
Addressable patients (40%)	37,136	37,136	37,136	37,136	37,136	37,136	37,136	37,136	37,136	37,136	37,136	37,136
Discontinuations due to Aes	4,456	4,456	4,456	4,456	4,456	4,456	4,456	4,456	4,456	4,456	4,456	4,456
Market share	0,2%	2%	6%	10%	16%	20%	23%	26%	28%	30%	30%	30%
Volume	65	654	1,961	3,268	5,229	6,536	7,516	8,497	9,150	9,804	9,804	9,804
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 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	750	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 (EURk)	3,691	33,412	92,735	152,059	240,294	299,117	343,235	387,352	416,764	446,176	446,176	446,176

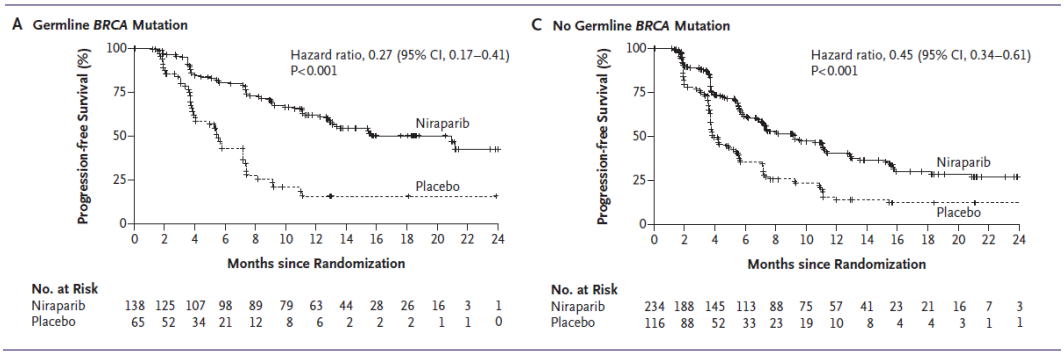
Source: Bryan, Garnier & Co ests.

2.3. PARP inhibitors: Promising but see you again (and more in-depth) next year

Beyond CDK4-6 inhibitors, another new class was under the spotlight: PARP inhibitors. However, our guess is that these will be even more the case next year as much more evidence will be available to assess their value in ovarian and breast cancer. This is all the more true as olaparib was unfortunately in the focus for a trial called GOLD where it failed to reach the pre-specified primary endpoint and the conclusion is that the issue is the reflection of a mistake in the design of the study. There is a strong correlation in the literature between ATM cell status or p53 function and PARP inhibition. Although it was clearly confirmed in phase II, where olaparib came out with very encouraging data, the phase III GOLD only included 18% of patients with ATM-negative tumours (vs 50% in phase II), translating into an overall benefit of 1.9 months in terms of median OS with a p-value of 0.0262 when 0.025 was required for statistical significance. The dose and the CT (paclitaxel vs irinotecan) used were also questioned.

In contrast with GOLD, the strong NOVA study results were also presented that were investigating Tesaro's PARP inhibitor in maintenance therapy for recurrent ovarian cancer and they were simply outstanding irrespective of the subgroups, i.e. with or without BRCA mutation. That said, it is fair to say that, in non-gBRCA mutated patients, the efficacy was driven by HRD-positive patients. In gBRCAm and non-gBRCAm but with HRD+, median PFS was 3-4 fold higher than placebo. Importantly though, it looks like the more intense the prior platinum-based therapy the better the results, confirming that platinum response correlates to the response to PARP inhibitors. This might question the use of PARP inhibitors in naïve patients (where combinations may be envisaged, like with WEE-1 inhibitors at AstraZeneca). There will be much more data to share on PARP inhibitors in 2017, including in breast cancer.

Fig. 15: Key efficacy results from the NOVA phase III trial



Source: NEJM

BRYAN, GARNIER & CO

INDEPENDENT RESEARCH UPDATE

19th October 2016

Ipsen

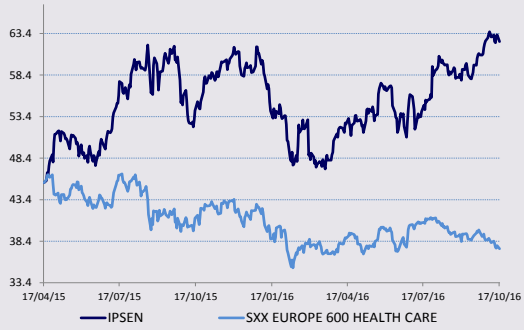
Cabometyx AND Somatuline to transform Ipsen

Healthcare

Fair Value EUR72 vs. 67 (price EUR63.16) **BUY-Top Picks**

Bloomberg	IPN FP
Reuters	IPN.PA
12-month High / Low (EUR)	63.6 / 47.1
Market capitalisation (EURm)	5,259
Enterprise Value (BG estimates EURm)	5,342
Avg. 6m daily volume ('000 shares)	75.30
Free Float	32.0%
3y EPS CAGR	15.6%
Gearing (12/15)	-8%
Dividend yield (12/16e)	1.35%

YE December	12/15	12/16e	12/17e	12/18e
Revenue (€m)	1,444	1,581	1,753	1,925
EBIT (€m)	322.48	358.22	413.20	488.09
Basic EPS (€)	2.31	2.96	3.29	3.96
Diluted EPS (€)	2.78	3.05	3.60	4.29
EV/Sales	3.6x	3.4x	3.0x	2.6x
EV/EBITDA	14.1x	12.6x	10.8x	8.9x
EV/EBIT	16.0x	14.9x	12.7x	10.4x
P/E	22.7x	20.7x	17.5x	14.7x
ROCE	22.6	18.5	20.8	23.9



The success of Somatuline in the US, although still in an early phase, has been identified as a key and transformative outcome for Ipsen but it has yet to be determined how high it can go. More controversial is the influence of Cabometyx because competition is fiercer and also because Ipsen only has rights outside North America. However, we have been reassured by what we heard at the ESMO congress.

- Cabometyx was much discussed at ESMO and even benefited from a presentation of the CABOSUN phase II data in 1L mRCC in the Presidential session. We believe it is fair to look at 2L mRCC and 1L mRCC as two distinct opportunities and to say that the jury is largely still out when it comes to determining future guidelines in 1L and 2L if only because many clinical studies are still ongoing. In order to stay on the safe side, we have assumed that cabozantinib would play the role of preferred TKi in 2L while we keep any 1L influence as pure upside, be it in monotherapy or in combination. We are ready to revisit the case should CABOSUN data be accepted for filing by EMA in 2017. With nivolumab, avelumab, pembrolizumab and atezolizumab all investigated in trials as we write, we see it as premature to bet on any meaningful use in 1L. However, we do not believe 1L is required for cabo to reach USD500m PS in Ipsen's territories if a good launch is executed in key countries.

- There was nothing new and game-changing for Somatuline at ESMO as there was with Cabometyx but interesting discussions took place about the evolving evidence of treatment need for patients with NET based on stage, status or markers. The opportunity was offered to measure the impact CLARINET had on clinical practice in terms of willingness to treat compared to a watch-and-wait approach. A short conclusion would be that active surveillance is still deserved but the number of cases where it is required have reduced significantly. This underlying trend, together with enriched data package, should keep Somatuline on a growth trajectory for some time.

- In conclusion, we feel comfortable to adjust the sales of Somatuline and Cabometyx upwards to respectively EUR850m (from EUR800m) and EUR450m (from EUR300m). Our FV jumps from EUR67 to EUR74.

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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	1,581	1,753	1,925	2,082
Change (%)	*0.5%*	*4.1%*	*13.3%*	*9.5%*	*10.9%*	*9.8%*	*8.2%*
Adjusted EBITDA	236	311	366	425	487	569	639
EBIT	211	261	322	358	413	488	552
Change (%)	*7.4%*	*23.8%*	*23.8%*	*11.1%*	*15.3%*	*18.1%*	*13.1%*
Pre-Tax profits	201	206	237	338	375	452	520
Tax	(59.3)	(53.8)	(49.8)	(94.6)	(105)	(127)	(146)
Profits from associates	0.0	1.9	2.5	0.0	0.0	0.0	0.0
Net profit	142	155	190	243	270	325	374
Restated net profit	115	183	228	250	295	352	402
Change (%)	*-25.1%*	*58.3%*	*24.9%*	*9.7%*	*18.0%*	*19.2%*	*14.3%*
Cash Flow Statement (EURm)							
Operating cash flows	209	240	305	280	343	405	460
Change in working capital	(21.1)	5.3	(81.1)	(10.1)	(23.9)	(24.5)	(22.4)
Capex, net	(42.0)	(47.4)	(50.0)	(66.7)	(73.5)	(80.5)	(86.9)
Dividends	0.79	0.77	0.84	1.1	1.3	1.2	1.2
Net debt	(25.4)	(70.5)	(102)	82.6	(15.2)	(180)	(389)
Free Cash flow	146	198	174	203	246	300	351
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	12.9	111	276	485
current assets	602	672	810	687	831	1,044	1,297
Total assets	1,565	1,713	1,938	2,079	2,264	2,517	2,810
L & ST Debt	374	419	450	451	474	497	519
Shareholders' funds	974	1,068	1,226	1,378	1,540	1,769	2,040
Total Liabilities	592	645	712	701	724	748	769
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	22.66	23.57	25.36	26.52
Tax rate	29.47	26.07	20.97	28.00	28.00	28.00	28.00
Net margin	11.07	11.60	12.51	14.60	14.71	16.17	17.23
ROE (after tax)	14.57	14.47	15.52	17.66	17.56	18.39	18.34
ROCE (after tax)	15.41	18.49	22.59	18.52	20.77	23.86	26.29
Gearing	(2.61)	(6.60)	(8.29)	5.99	(0.99)	(10.19)	(19.07)
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	2.96	3.29	3.96	4.55
Restated EPS	1.85	2.22	2.78	3.05	3.60	4.29	4.90
% change	*5.8%*	*19.9%*	*25.3%*	*9.7%*	*18.0%*	*19.2%*	*14.3%*
BVPS	11.51	12.99	14.95	16.80	18.78	21.57	24.88
Operating cash flows	2.47	2.92	3.72	3.42	4.18	4.94	5.61
FCF	1.73	2.41	2.12	2.48	2.99	3.66	4.28
Net dividend	0.80	0.85	0.85	0.85	1.16	1.25	1.40

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

1. Cabometyx is swing factor number 1

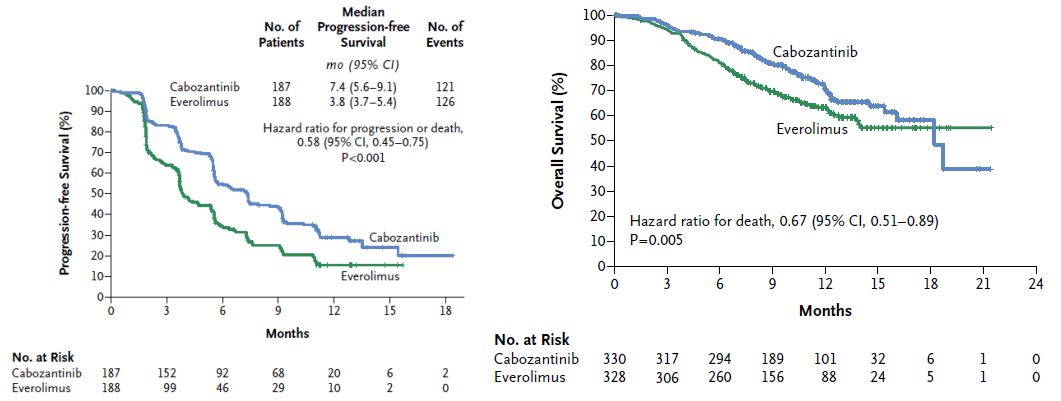
1.1. Cabometyx: a no-brainer in 2L mRCC?

1.1.1. Very consistent clinical results

When Ipsen unveiled the terms of its agreement with Exelixis earlier this year, there was a high degree of scepticism about the degree of uniqueness the company had seen in the data room it had had access to in order to assess the value of cabozantinib in mRCC. At the end of the day, cabozantinib was nothing more than another TK inhibitor, although admittedly with slightly different targeted receptors. At a time when IO drugs give the impression that everything else is old medicine, even though we are among those who say that it is not the end of CT, it was difficult to see cabozantinib as a disruptive agent.

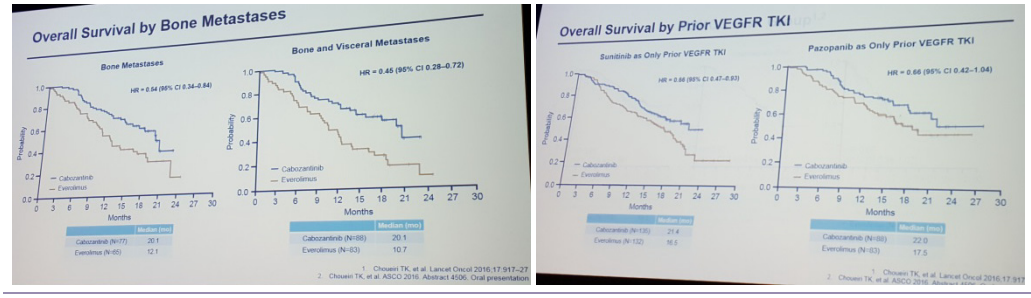
About six months later, the situation has dramatically changed. Detailed data have been presented, first at ASCO and again at ESMO from the METEOR phase III trial in 2L mRCC and they show how consistent they are across the various subgroups (see Fig. 2). On this basis, the drug has been approved in record time both in the US by the FDA and also in Europe by the EMA. It is now also part of the key recommended guidelines set by the NCCN and more recently by the ESMO guidelines as reflected in *Ann. Oncol.* 2016 Sep, 27.

Fig. 1: mPFS and mOS data from the METEOR phase III trial



Source: NEJM

Fig. 2: Read-out of mOS data by bone met status (left) or prior VEGFr (right)



Source: pictures from ESMO 2016

1.1.2. A step change in 2L mRCC

As reflected by the new guidelines issued, nivolumab and cabozantinib are the two new and equally treated options for 2L mRCC, to replace the previously used therapies which were usually either sorafenib (a VEGFR inhibitor) or everolimus (an mTOR inhibitor). There is little doubt that the two drugs will quickly take over from the old ones, if only because they have both established a mOS-based superiority when previously this had never been achieved (always only mPFS was positive).

That said, the question obviously for Ipsen is how much market share cabozantinib can take compared to nivolumab short term and maybe compared to IO in general at a later stage. When this was put to specialists in the field, as was done during the NET symposium at ESMO, the answer was that about a third of the physicians would use cabozantinib in the majority of their patients in 2L whereas half would use it in less than 25% to none of their patients. In any case, we are comfortable with our PS estimate based on a 30% market share in 2L mRCC in 2025, suggesting that most of the rest would be taken by IO drugs.

However, it is fair to say that, from here, it is difficult to move on splitting the market into two distinct parts without any read-across through the various lines of treatment.

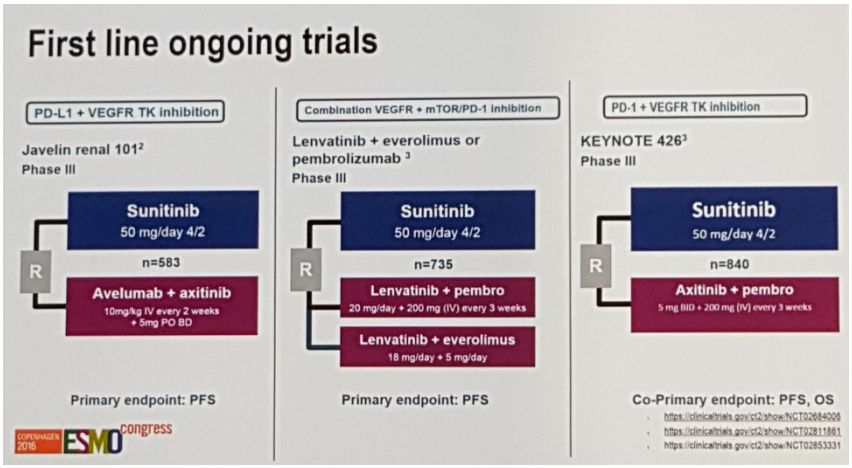
1.2. Can SoC also change in 1L mRCC?

1.2.1. First data in 1L suggest upcoming changes

With no change to 1L mRCC standard-of-care (SoC), it would be quite easy to make assumptions about 2L mRCC in terms of market share because the picture would stay more or less at it is today, adding that a third-line would likely be a split between axitinib and the newly-approved combination of everolimus and Eisai's lenvatinib.

But there are currently too many phase III trials assessing new drugs and/or combinations in 1L mRCC to expect the SoC to remain unchanged. We have identified four different PD-1 or PD-L1 targeting agents in such trials as we write (pembro appears twice), including two that are now closed to recruitment (nivolumab + ipilimumab vs sunitinib and atezolizumab + bevacizumab vs sunitinib) while three trials are still recruiting patients (see Fig.3).

Fig. 3: Three IO-based phase III recruiting in 1L mRCC



Source: pictures from ESMO 2016

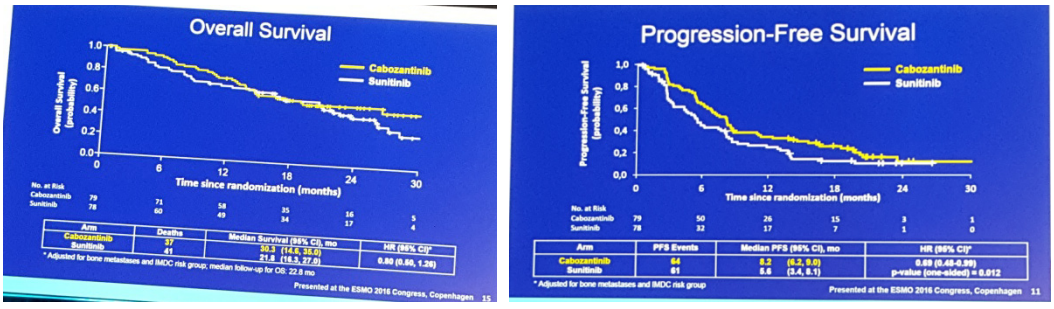
It is fair to stress that none of the ongoing 1L mRCC trials includes cabozantinib as a combination agent, whereas competitor number 1 in the class, namely axitinib, is included in two and recently-approved lenvatinib in one. This could be seen as a weakness by physicians not to see cabozantinib included in study protocols investigating combinations of drugs because, considering the very high level of drop-out rate between 1L and 2L (see post-ESMO report), i.e. more than 50%, it is very likely that the most effective treatment will be used in 1L since physicians cannot be sure if any single patient will benefit from a 2L treatment at some point. Many physicians at ESMO have expressed interest in seeing a trial designed in such a way to compare Cabo/Nivo to Cabo then Nivo but it is uncertain whether Exelixis/Ipsen will agree to finance this potentially large and expensive trial. The enthusiasm about combinations partially comes from phase I data shared in 24 patients with genito-urinary tumours and treated with cabo-nivo or cabo-nivo-ipi and resulting in a remarkable 43% overall response rate in a heavily pre-treated population (10 had more than 4 previous lines of therapy). In bladder cancer only, 6 out of 8 patients had responses, prompting Exelixis to move into phase II with cabo 40 mg-nivo 3 mg/kg in bladder cancer after a first-line with atezo.

But here comes CABOSUN into play.

1.2.2. Can CABOSUN open the 1L mRCC market to cabozantinib?

Since Ipsen acquired the ex-US, ex-Canada and ex-Japan rights of cabozantinib, it has been lucky enough to see the phase II trial CABOSUN also reporting positive results. As with other ongoing trials in 1L mRCC, the primary endpoint was an improvement in median PFS compared to SoC sunitinib scheduled as recommended by the label, i.e. 4 weeks On and 2 weeks Off treatment.

Fig. 4: Main data from CABOSUN presented at ESMO



Source: pictures from ESMO 2016

It is worth also keeping in mind that only patients with intermediate to poor prognosis were included in order to save time and to collect data quickly (it is estimated that median survival for patients with mRCC of favourable risk is almost 18-20 months longer than those with intermediate risk). Unlike some other trials, CABOSUN allowed inclusion in the trial of patients with bone metastases and in the end, 36% of those effectively recruited had bone metastases.

The results which were presented at ESMO in detail and which are part of the core part of this sector note are good across the various subgroups, including those reflecting the poorer prognosis, i.e. with bone mets, after nephrectomy or ranked as ECOG 2. It is, however, true that discussant Bernard Escudier had mixed comments about CABOSUN results to say the least, asking for a phase III trial before being fully comfortable to prescribe cabozantinib in first-line. This was the result of a non-statistically significant median OS benefit which came up from 21.8 months to 30.3 months (HR=0.80, [0.50-1.26]) after a follow-up of only 21-22 months when probably 6-12 more months would be required.

Although it was still rather early days for Exelixis and Ipsen to comment on the regulatory pathway for 1L RCC, they were hopeful they might be able to file on the basis of the CABOSUN phase II data. The full dataset will soon be transferred from the Alliance that ran the trial for Exelixis, which will decide whether it is solid enough to be filed to the FDA. Ipsen will have the same data with a slight delay for a potential submission in Europe, which could take place by the end of H1 2017. Because the headlines were already in the original package discussed for 2L mRCC approval, new Head of Regulatory Affairs Stephane André (who comes from Roche) believes that a filing under the "variation" procedure in the EU is possible, lasting 90 days, offering a potential approval in 1L by the end of 2017, which would be a nice surprise and offer a meaningful upside to the numbers.

Ipsen's confidence in being able to file cabozantinib in 1L mRCC is actually reinforced by the recent approval of Eisai's lenvatinib (in combination with everolimus) based on a 103-patient large phase II trial in 2L mRCC. Moreover, in 1L mRCC SoC has not changed for years and it makes little doubt that cabozantinib compares favourably to sunitinib. At some point, combinations will be able to do even better but this will come at a later stage. It is fair to write, however, that when comparing CABOSUN to HOPE, hazard ratios were not the same, clearly favouring the combination in 2L (HR=0.55 vs 0.80 for mOS).

1.3. Cabometyx: changes to our model

All in all, in spite of Pr Escudier's caution, data presented in 2L and 1L represent high hopes for cabozantinib to take a meaningful share of the mRCC market alongside IO drugs. The worst case is a shared SoC position in 2L mRCC but we believe it is fair and reasonable to expect cabo to also take a portion of the 1L mRCC market, if only in patients with bone mets and poor prognosis where it could be used in combination. The key question could be whether it is best to use it front-line to induce an immune permissive environment before introducing an IO drug or later when resistance develops to help return to a form of response. To this question, some physicians were simply stressing that between 40% and 60% of patients treated in 1L mRCC do not reach 2L, hence the necessity to use the best available option in 1L.

That said, for modelling purposes, we have decided to stay on the cautious side and to take the following key hypothesis:

- 84,400 patients are newly diagnosed for metastatic renal cell carcinoma in Europe each year (2013 data). We have added to this number 10% to reflect some kind of market opportunity outside the EU and mainly in Asia and Australia;
- we have taken as the addressable market for cabozantinib only 40% of this population to represent 2L of therapy;
- we have excluded 12% of those to reflect discontinuations due to adverse events (same rate as in trials);
- our assumption is that cabozantinib will be able to grab a gradually increasing market share of 10% (in 2019), then 20% (in 2021) and up to 30% (in 2025);
- the list price is set at around EUR6,000 per month. We have assumed a 15% discount in Ipsen's territories and duration of treatment based on mPFS;
- sales in MTC are stabilising at around EUR5m per annum as of 2019.

On this basis, sales of cabozantinib would reach EUR150m in 2019, EUR300m in 2021 and peak in 2025 at close to EUR450m.

Fig. 5: Cabozantinib sales model for Ipsen's territories

	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
Incidence Europe RCC	84,400	84,400	84,400	84,400	84,400	84,400	84,400	84,400	84,400	84,400	84,400	84,400
10% extra incidence for ROW	8,440	8,440	8,440	8,440	8,440	8,440	8,440	8,440	8,440	8,440	8,440	8,440
Addressable patients (40%)	37,136	37,136	37,136	37,136	37,136	37,136	37,136	37,136	37,136	37,136	37,136	37,136
Discontinuations due to Aes	4,456	4,456	4,456	4,456	4,456	4,456	4,456	4,456	4,456	4,456	4,456	4,456
Market share	0,2%	2%	6%	10%	16%	20%	23%	26%	28%	30%	30%	30%
Volume	65	654	1,961	3,268	5,229	6,536	7,516	8,497	9,150	9,804	9,804	9,804
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 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	750	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 (EURk)	3,691	33,412	92,735	152,059	240,294	299,117	343,235	387,352	416,764	446,176	446,176	446,176

Source: Bryan, Garnier & Co ests.

Fig. 6: Royalties to be paid by Ipsen to Exelixis

USD000	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027
2%	82	735	1 000	1 000	1 000	1 000	1 000	1 000	1 000	1 000	1 000	1 000
12%			6 232	18 000	18 000	18 000	18 000	18 000	18 000	18 000	18 000	18 000
22%				3 771	25 109	39 334	50 002	60 671	67 784	74 896	74 896	74 896
26%												
Total royalties (USD, 000)	82	735	7 232	22 771	44 109	58 334	69 002	79 671	86 784	93 896	93 896	93 896
Royalties (EUR)	74	668	6 579	20 716	40 128	53 069	62 775	72 481	78 952	85 422	85 422	85 422
As a % of sales	2%	2%	7%	14%	17%	18%	18%	19%	19%	19%	19%	19%

Source: Bryan, Garnier & Co ests.

2. Somatuline to stay on a strong path

2.1. An increasing underlying opportunity

Neuroendocrine tumours (NETs or carcinoid tumours) are described as rare, slow-growing and heterogeneous neoplasms (notably by their embryonic origin in the foregut, the midgut or the hindgut) which develop in silence but then, after some time, become symptomatic and metastases. Some reports say that about 60% of NETs are diagnosed at an advanced stage and that overall median survival for patients with advanced NET is 33 months (Van Cutsem, 2013).

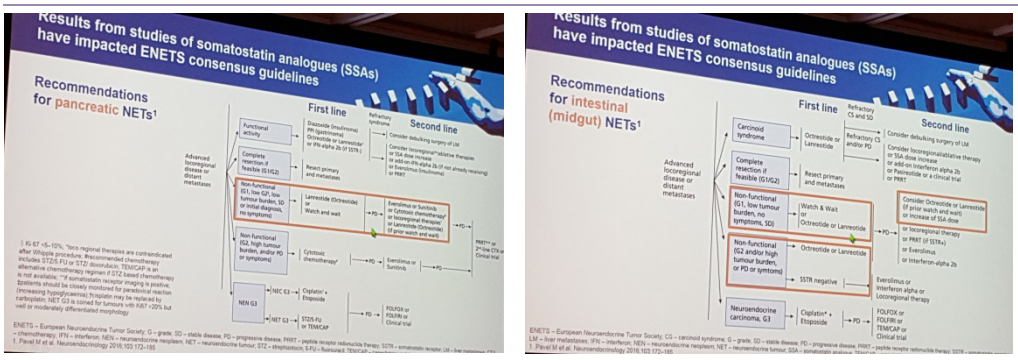
Described as rare, NET has nevertheless seen its incidence sharply increasing over recent decades and the latest updated statistics unveiled at the NANETS conference in March 2016 reported another increase. It was between 1 and 2 cases per 100,000 individuals per year in the 1970s and 1980s but then jumped to 3/100,000 in the early 1990s and above 4 at the end of the 1990s, above 5/100,000 at the early 2000s and it is now close to 7/100,000 (exactly 6.98/100,000 per year). Maybe this is a reflection of a continuous change in behaviour and dietary habits but it us more likely to be the result of a better understanding of the disease, an improvement in the diagnosis and in the treatments available.

Not only has the market opportunity increased for drug companies working in the field as a consequence of the progressing incidence of the disease but available options have remained limited, evidence that treating earlier is better has made progress and attempts to stratify have failed.

Somatostatin analogues (SSAs) are the cornerstone of therapy for patients with NETs of GI or pancreatic origin, first to treat the symptoms of excessive hormone secretion and more recently also to prevent progression (anti-proliferative effect). In the Western world, the primary location of NET is in the GI tract (about 60%), whereas lung represents about 30%.

For some time, a distinction was made between functional and non-functional NETs that now tends to reduce in the algorithm of treatment as shown in Fig.7. Functional NETs are defined by the existence of a clinical syndrome caused by the excess secretion of hormone and it is estimated that about one fifth of patients with carcinoid tumours develop carcinoid syndrome, characterised by flushing, diarrhoea, bowel disturbance or respiratory problems. Non-functional NET has no specific clinical syndrome although peptides and neuroamines are produced.

Fig. 7: ENETS guidelines reflect more favourable recommendations for SSAs

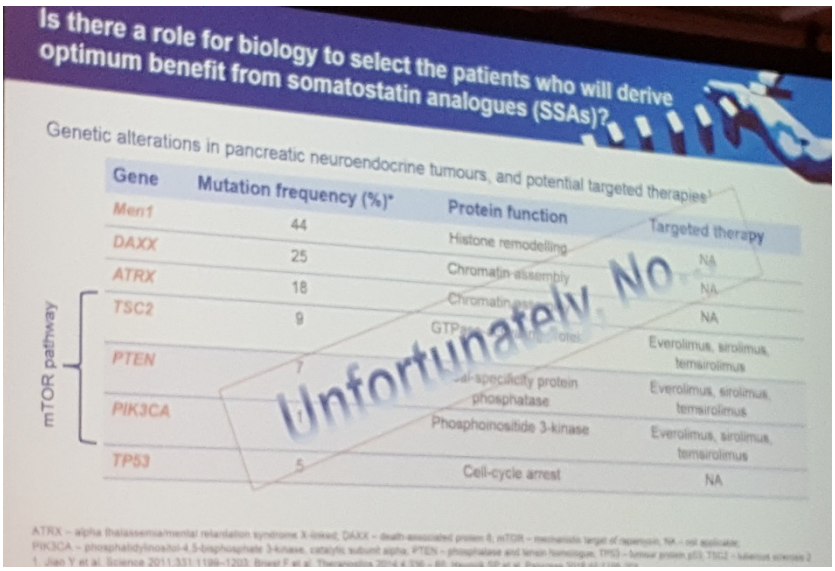


Source: pictures from ESMO 2016

SSAs are undisputed SoC in functional GEP-NET but recent data have also participated in discussing more their use in non-functional GEP-NET where active surveillance (also called "watch and wait strategy") was often and commonly in practice. From this perspective, the CLARINET phase III study played a key role in expanding the use of SSAs in non-functional GEP-NET where, as illustrated on the left picture of Fig.7, lanreotide has a preferred status over octretide in managing the disease even with low tumour burden and irrespective of the grading. It is left to the physician to decide whether to treat or not, depending mainly on a subjective assessment.

The main purpose of a symposium dedicated to NET at the ESMO meeting was to try to identify who might benefit from treatment vs no treatment. And a clear conclusion was at least that no biomarker was really effective to help the physician make his decision: patient status, disease status, grading, tumour burden, primary site do not make any difference when trying to be discriminant with SSA use (see Fig.8). Moreover, they are the least toxic drugs that can be used to treat NETs.

Fig. 8: No relevant biomarker exists to detect who is eligible to SSA



Source: picture from ESMO 2016

In the end, everyone agreed that "watch and wait" was a less and less relevant option with regards to recent data collected. That said, there are still some cases where it is worth watching without treating and this is in particular when the patient has low grade NET, limited to no liver involvement and even more if he is over 70 or 80.

2.2. Building a blockbuster is no longer out of reach

In the context described in the previous section, Somatuline appears very well positioned, although it can't – unlike Novartis's sandostatine – play the synergy with other products in the field of NETs (like an mTOR inhibitor).

To a certain extent, the point is not even to try to play one against the other because Novartis and Ipsen are working in the same direction to make SSAs more popular in the treatment of NETs. As said before, CLARINET has enlarged the market and, even if all physicians are not ready to treat all patients as early as possible, there is a clear move towards "earlier is better".

Although it has grown fast and steadily in the US since it obtained its first approval in NET and since Ipsen made itself ready for launch, Somatuline only captured about 12% market share in the US at the end of Q2 2016, exceeding the USD200m mark on an annual basis. So there is still a very significant upside for the brand and, although the objective was first to grow the market and to capture the newest part of it, our understanding is that Ipsen is now also trying to think how it could also grab market share from Sandostatine. For that, the group is still reinvesting significantly behind the drug to increase physicians' awareness about the brand and the clinical results and to enlarge the base of prescribing doctors.

At the end of 2016, Sandostatine will still be more than three times bigger than Somatuline and close to four times bigger in the US.

Competition around Sandostatine potentially impacting Somatuline

Over the next few years, there is no question that Somatuline will continue to post strong growth, largely driven by the continuous penetration in the US market. But beyond that period, it is less clear how well Somatuline can do and it is fair to say that it might depend on a number of factors that are not fixed yet: first is a bioequivalent version of Sandostatine that could reach the market in 2018 and this might have implications in terms of relative positioning of Somatuline vs octreotide if prices diverge meaningfully; second would be a new formulation of Sandostatine, longer-acting, that would not only impact the market *per se* but make Novartis care much about its franchise and reinvest behind it; and third new players could also join the field although we have not heard about anything newly disruptive progressing fast and approaching the market soon.

A word nevertheless about Advanced Accelerator Applications (AAA) which is working on a Lu-177-labelled somatostatin analogue peptide called Lutathera, developed in GEP-NET (first phase III trial NETTER-1 has seen first results presented at ASCO GI in January 2016). The results are quite good actually but we would make two observations: first, AAA is investigating Lutathera in patients with advanced NET no longer responding to an SSA in comparison with intensification of treatment (dose escalation). Even though this is an existing strategy once first-line fails, we see bevacizumab and everolimus as already existing companion drugs for SSAs, the difference being that it could replace it rather than combine with it. But, the second point is that radiotherapy is always difficult and heavy to handle and so we would see it as being reserved for a last rescue line of treatment.

Several trials ongoing with Somatuline too

Interestingly, we cannot rule out use of Somatuline at twice the standard dose when the 120 mg monthly dose no longer prevents progression but it has not been well documented and we doubt it is widely performed, unlike double-dose octreotide. That said, it is currently being investigated in a phase II trial called CLARINET FORTE which compares the 120 mg lanreotide autogel monthly dose to the same dose but administered twice a month in 100 patients with progressing grade 1-2 GEP-NET. The study is due to report results in 2019.

A French collaborative group is also conducting a study to compare Somatuline 120 mg monthly with placebo in maintenance therapy for patients with non-resectable duodeno-pancreaatic NET after a first-line of therapy. This is a phase II/III trial (REMINET) whose first read-out is expected in mid-2017 from the first phase (222 patients) based on survival and progression-free survival at 6 months.

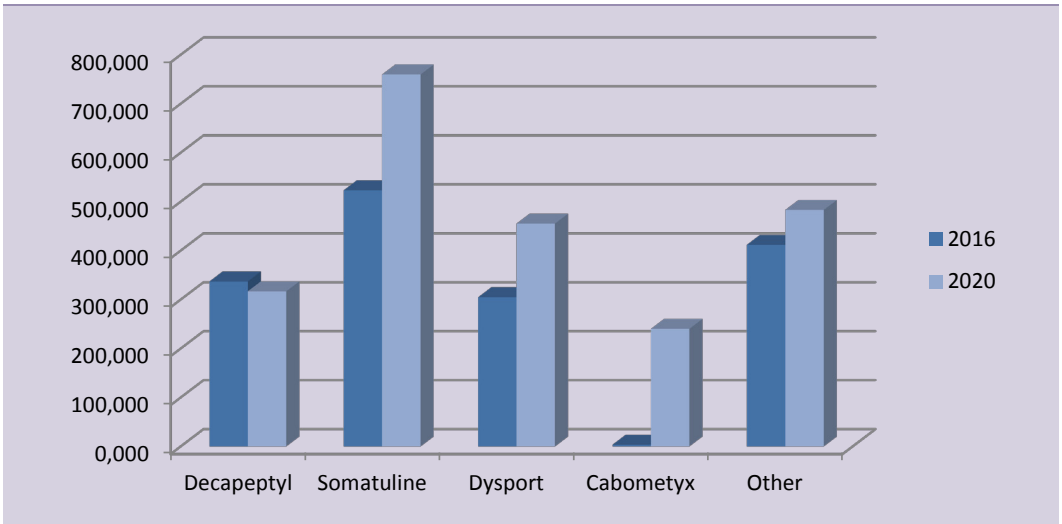
Last but not least, as written before, lung is after the GI tract the most common primary location of NET and so it is logical to find also an ongoing trial to assess lanreotide autogel 120 mg monthly in lung NET. The phase III trial is called SPINET and is recruiting 216 patients to compare the drug vs placebo on top of BSC in first-line of treatment. The primary endpoint is median PFS. The primary completion date is mid-2019 (175 events required).

3. Conclusion

Our attendance at several sessions dedicated to either NET or mRCC during the last ESMO meeting in Copenhagen has reinforced our confidence in both Somatuline and Cabometyx reaching higher peak sales than we had so far anticipated in our sales models.

Over the full year 2016, we expect Ipsen to achieve total revenues of close to EUR1.6bn, of which the so-called Top 4 drugs will represent 74% of the total. Obviously, without the meaningful effort to build-up an oncology sales force in Europe to launch Cabometyx successfully, the operating margin would have reflected this significant mix change in 2016 already. Now, with this investment being even more front-loaded than initially expected as the approval came early and because it is key to gain time against nivolumab, the leverage is anticipated to be massive as of 2017. We believe it is possible to see the operating margin going up by about 500bp by 2020 despite partial reinvestments and some margin erosion in Primary Care.

Fig. 9: Contribution of the key 4 drugs to Ipsen's sales



Source: Bryan, Garnier & Co ests.

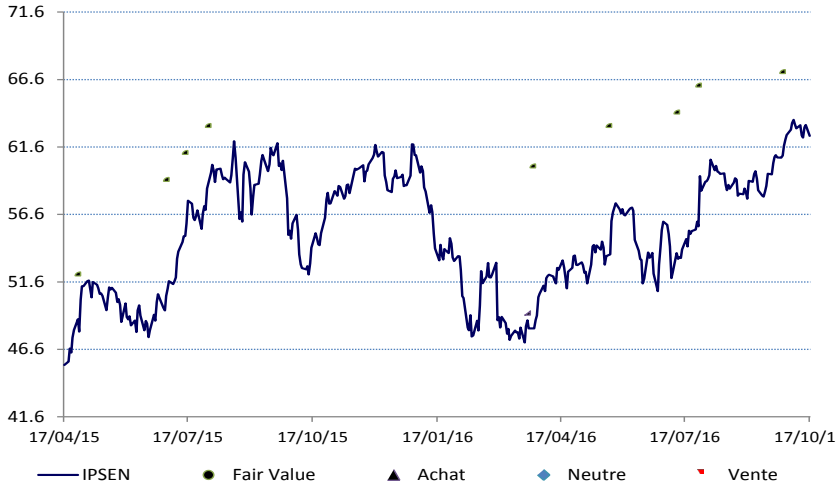
A new FV of EUR72

Based on our new assumptions for Somatuline and Cabometyx, **we derive a FV of EUR72** without introducing any change to the key hypothesis for our DCF calculation, i.e. a RFR of 1.6%, an ERP of 7.0%, a beta of 1x (similar to Actelion's, although the historical beta calculated over 3-5 years is reported to be in the range of 0.7-0.8x, i.e. in line with large cap pharmaceutical companies). In the end, the WACC used is 8.6%. If we used a beta of 0.9x instead of 1x, the FV would be up by EUR8 to EUR80.

We reiterate our BUY rating on Ipsen which remains in our Top Pick List for the quarter.

Price Chart and Rating History

Ipsen



Ratings		
Date	**Ratings**	**Price**
29/03/2016	BUY	EUR48,75
01/03/2016	Under review	EUR53,02
04/11/2014	BUY	EUR29,01
02/09/2013	NEUTRAL	EUR28

Target Price	
Date	**Target price**
29/09/2016	EUR67
29/07/2016	EUR66
13/07/2016	EUR64
24/05/2016	EUR63
29/03/2016	EUR60
03/08/2015	EUR63
17/07/2015	EUR61
03/07/2015	EUR59
29/04/2015	EUR52
16/04/2015	EUR46,5
14/04/2015	EUR48
17/12/2014	EUR46
01/09/2014	EUR41
11/04/2014	EUR36
07/01/2014	EUR33
02/09/2013	EUR29,5
14/06/2013	EUR30,5
17/01/2013	EUR29

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

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BUY ratings 56,7% NEUTRAL ratings 31,2% SELL ratings 12,1%

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