BRYAN, GARNIER & CO

INDEPENDENT RESEARCH UPDATE

19th October 2016

Ipsen

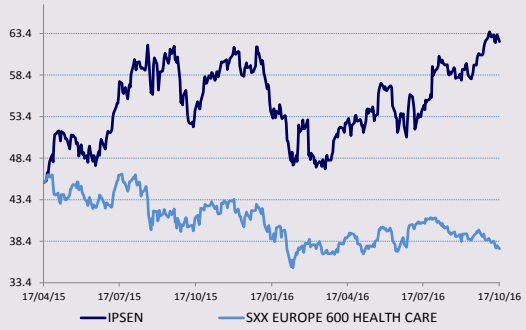
Cabometyx AND Somatuline to transform Ipsen

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.

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1. Cabometyx is swing factor number 1

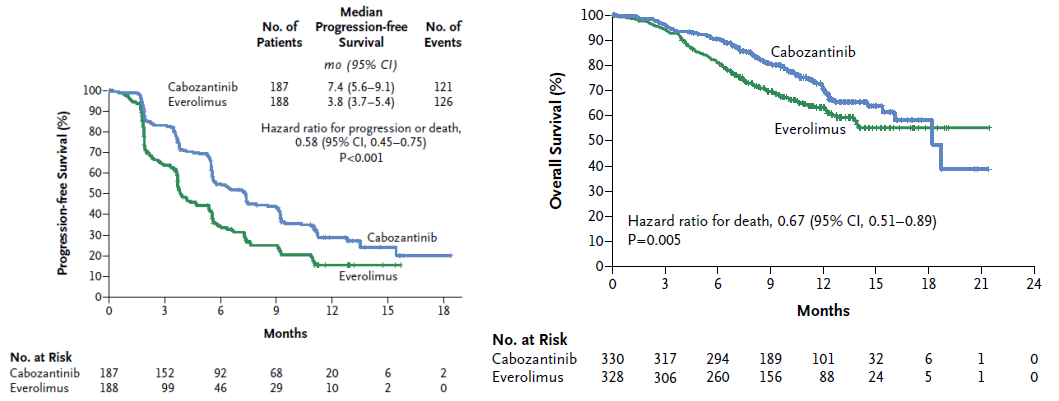
1.1. Cabometyx: a no-brainer in 2L mRCC?

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.

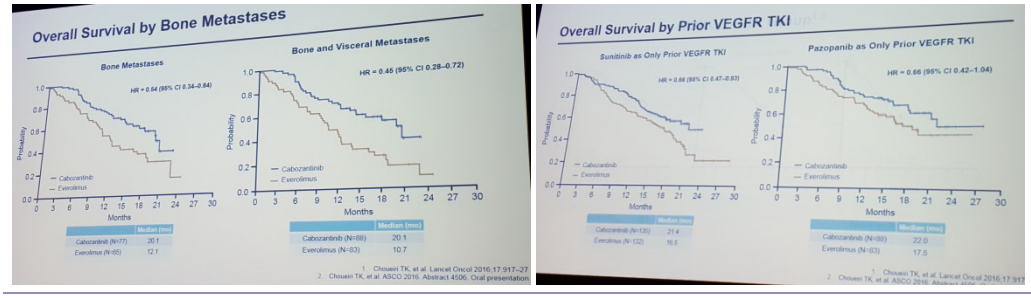
About six months later, the situation has dramatically changed. Detailed data have been presented, first at ASCO and again at ESMO from the METEOR phase III trial in 2L mRCC and they show how consistent they are across the various subgroups (see Fig. 2). On this basis, the drug has been approved in record 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.

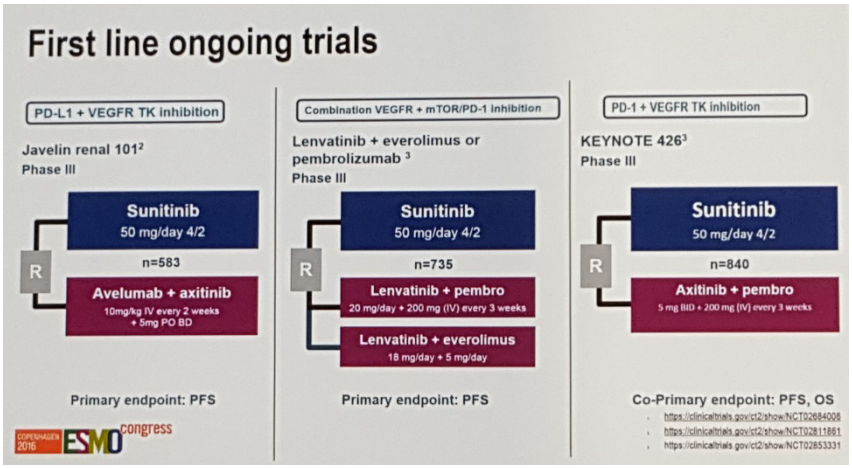
1.2. Can SoC also change in 1L mRCC?

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

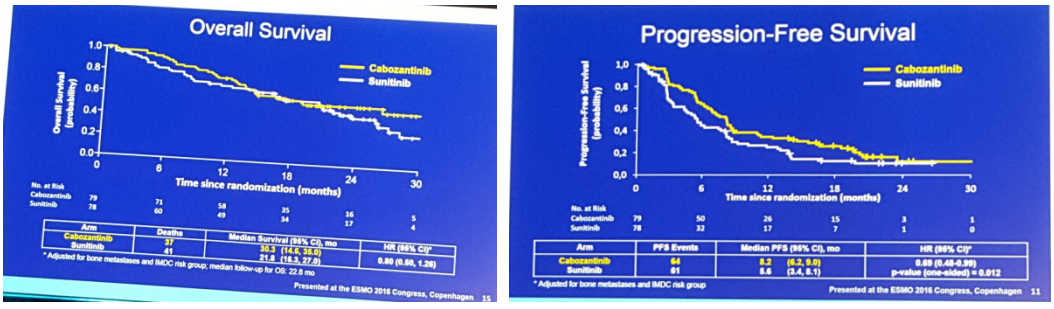
It is fair to stress that none of the ongoing 1L mRCC trials includes cabozantinib as a combination agent, whereas competitor number 1 in the class, namely axitinib, is included in two and recently-approved lenvatinib in one. This could be seen as a weakness by physicians not to see cabozantinib included 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).

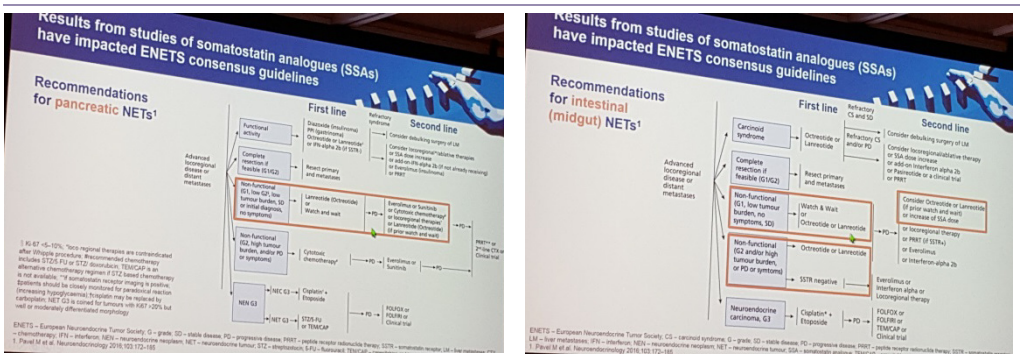
Described as rare, NET has nevertheless seen its incidence sharply increasing over recent decades and the latest updated statistics unveiled at the NANETS conference in March 2016 reported another increase. It was between 1 and 2 cases per 100,000 individuals per year in the 1970s and 1980s but then 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

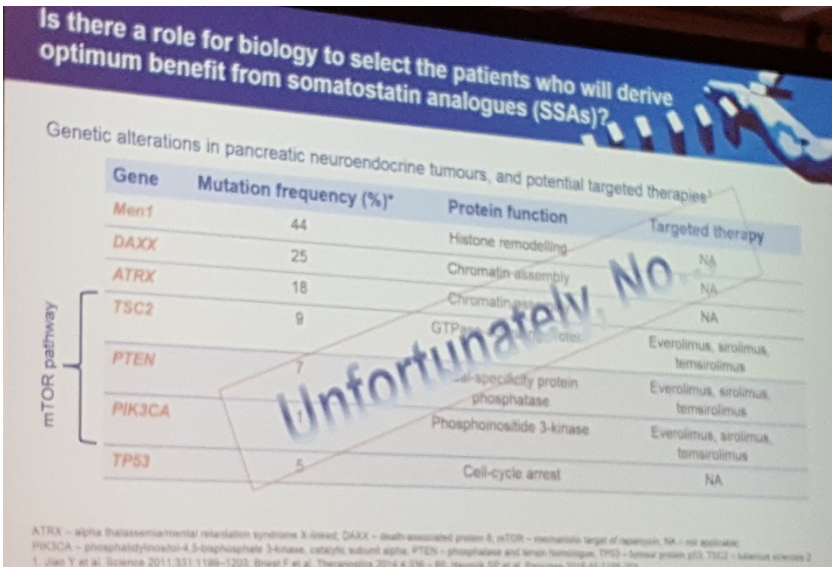


Source: pictures from ESMO 2016

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.

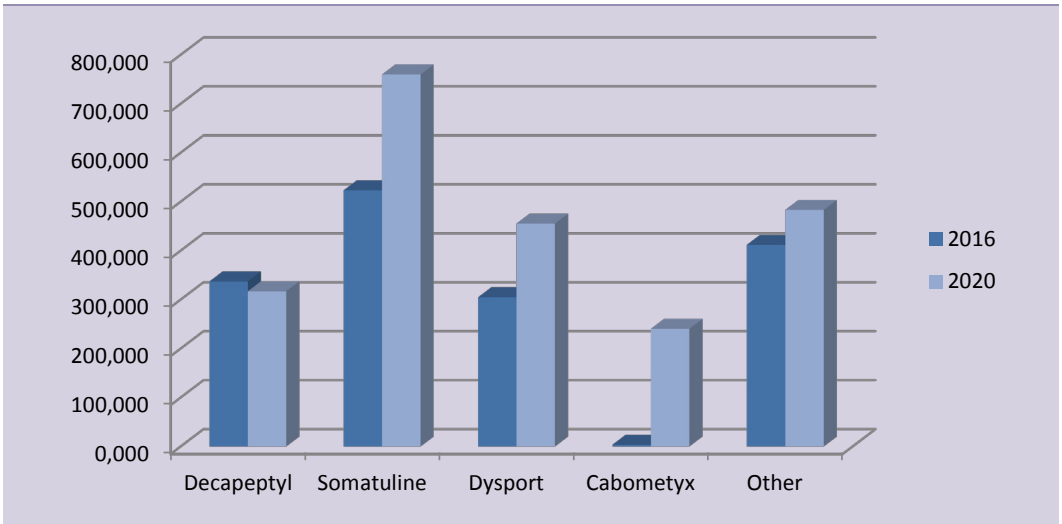
Last but not least, as written before, lung is after the GI tract the most common primary location of NET and so it is logical to find also an ongoing trial to assess lanreotide autogel 120 mg monthly in lung NET. The phase III trial is called SPINET and is recruiting 216 patients to compare the drug 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.

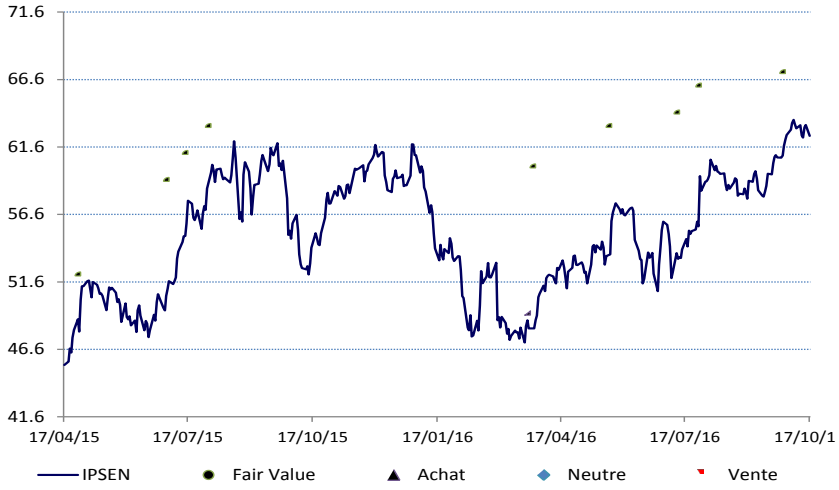
A new FV of EUR72

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

Bryan Garnier stock rating system

For the purposes of this Report, the Bryan Garnier stock rating system is defined as follows:

Stock rating

BUY — Positive opinion for a stock where we expect a favourable performance in absolute terms over a period of 6 months from the publication of a recommendation. This opinion is based not only on the FV (the potential upside based on valuation), but also takes into account a number of elements that could include a SWOT analysis, momentum, technical aspects or the sector backdrop. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

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SELL — Negative opinion for a stock where we expect an unfavourable performance in absolute terms over a period of 6 months from the publication of a recommendation. This opinion is based not only on the FV (the potential downside based on valuation), but also takes into account a number of elements that could include a SWOT analysis, momentum, technical aspects or the sector backdrop. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

Distribution of stock ratings

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

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