

Sector View

Healthcare

Feedback from ESMO – Part 1

	1 M	3 M	6 M	31/12/15
Healthcare	-2.8%	-5.0%	0.1%	-10.0%
DJ Stoxx 600	-3.1%	5.4%	3.5%	-7.2%

*Stoxx Sector Indices

Companies covered

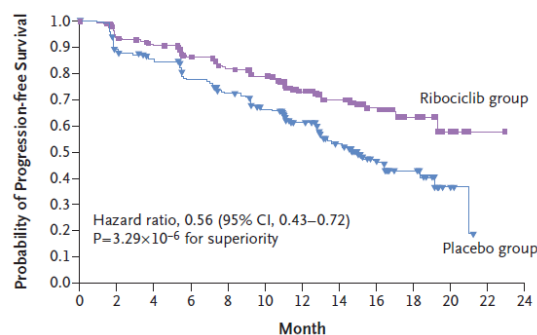
ABLYNX	BUY	EUR18
Last Price	EUR10.92	Market Cap. EUR665m
ACTELION	NEUTRAL	CHF180
Last Price	CHF167.3	Market Cap. CHF18,028m
ADOCIA	BUY	EUR90
Last Price	EUR51.99	Market Cap. EUR356m
ASTRAZENECA	BUY	5220p
Last Price	5086p	Market Cap. GBP64,339m
BAYER	NEUTRAL	EUR98
Last Price	EUR89.8	Market Cap. EUR74,260m
BIOMERIEUX	NEUTRAL	EUR130
Last Price	EUR132.55	Market Cap. EUR5,230m
BONE THERAPEUTICS	BUY	EUR30
Last Price	EUR10.54	Market Cap. EUR72m
CELLECTIS	BUY	EUR37
Last Price	EUR20.28	Market Cap. EUR717m
CELYAD	NEUTRAL	EUR21
Last Price	EUR19.26	Market Cap. EUR179m
DBV TECHNOLOGIES	BUY	EUR91
Last Price	EUR67.5	Market Cap. EUR1,627m
ERYTECH	BUY	EUR47
Last Price	EUR17.5	Market Cap. EUR139m
FRESENIUS MED.CARE	BUY	EUR94
Last Price	EUR74.4	Market Cap. EUR22,851m
FRESENIUS SE	BUY	EUR78
Last Price	EUR69.53	Market Cap. EUR38,028m
GALAPAGOS	BUY	EUR64
Last Price	EUR57.73	Market Cap. EUR2,665m
GENEURO	BUY	EUR18.2
Last Price	EUR7.05	Market Cap. EUR103m
GENMAB	BUY	DKK1600
Last Price	DKK1136	Market Cap. DKK68,443m
GLAXOSMITHKLINE	BUY	1810p
Last Price	1709p	Market Cap. GBP83,327m
INNATE PHARMA	BUY	EUR18
Last Price	EUR11.01	Market Cap. EUR594m
IPSEN	BUY	EUR67
Last Price	EUR62.98	Market Cap. EUR5,244m
KORIAN	NEUTRAL	EUR28
Last Price	EUR27.87	Market Cap. EUR2,235m
MORPHOSYS	BUY	EUR64
Last Price	EUR43.32	Market Cap. EUR1,150m
NOVARTIS	NEUTRAL	CHF87
Last Price	CHF76.55	Market Cap. CHF201,106m
NOVO NORDISK	NEUTRAL	DKK355 vs 360
Last Price	DKK270.3	Market Cap. DKK543,996m

At the end of the first few days of congress in Copenhagen, we would say that CDK4-6 were very much endorsed as new likely SoC in ER+ BC (which is good for Novartis, despite a position of challenger behind Pfizer), whereas the jury is still out in NSCLC about the size of the opportunity although Roche did the job with OAK (in 2L/3L). 1L is still very much open.

Highlights from day 1

If we had to take home with only one major idea from day 1, 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 Symposium of the MONALEESA-2 phase III results, the common conclusion is that CDK4-6 inhibitors work irrespectively of the subgroups. Different hypothesis have been tested, including p16 or Ki-67 status are predictive markers, but it 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 concluded by asking 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 tumors makes a difference or if they deserve being used across the board. But true is that the results are impressive when this compares 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.1: PFS results in MONALEESA-2 phase III trial (left) – Comparison of CDK4-6 inhibitors (right)



No. at Risk	334	294	277	257	240	226	164	119	68	20	6	1	0
Ribociclib	334	294	277	257	240	226	164	119	68	20	6	1	0
Placebo	334	279	264	237	217	192	143	88	44	23	5	0	0

Abemaciclib (LY-2835219)	Palbociclib (PD-0332991)	Ribociclib (LEE011)
CDK1: >1 μM	CDK1: >10 μM	CDK1: >100 μM
CDK2: >500 nM	CDK2: >10 μM	CDK2: >50 μM
CDK4: 2 nM	CDK4: 9-12 nM	CDK4: 10 nM
CDK5: ND	CDK5: >10 μM	CDK5: ND
CDK6: 5 nM	CDK6: 15 nM	CDK6: 39 nM
CDK7: 300 nM	CDK7: ND	CDK7: ND
CDK9: 57 nM	CDK9: ND	CDK9: ND

Nature Reviews | Clinical Oncology
O'Leary B, et al. Nat Rev Clin Oncol. 2016;13(7):417-430.

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 that presented also solid data in FALCON but with late benefit, 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 5 cases of febrile neutropenias), that are asymptomatic and usually manageable with treatment interruption. We would note however

ORPEA	BUY	EUR85
Last Price	EUR76.51	Market Cap. EUR4,595m
QIAGEN	BUY	EUR26
Last Price	EUR24.435	Market Cap. EUR5,857m
ROCHE HOLDING	BUY	CHF293
Last Price	CHF238.3	Market Cap. CHF167,421m
SANOFI	NEUTRAL	EUR83
Last Price	EUR68.8	Market Cap. EUR88,686m
SHIRE PLC	BUY	6900p
Last Price	5196p	Market Cap. GBP46,918m
UCB	NEUTRAL	EUR80
Last Price	EUR67.74	Market Cap. EUR13,176m
ZEALAND	BUY	DKK172
Last Price	DKK104.5	Market Cap. DKK2,723m

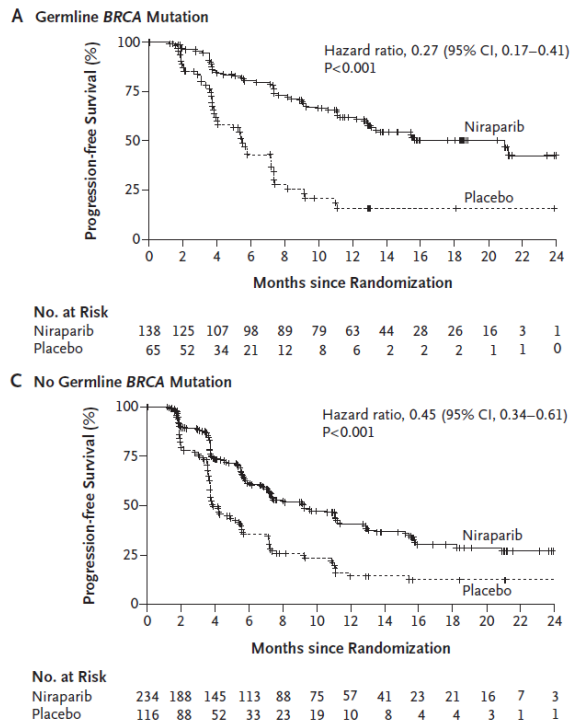
that there were 4 patients that met criteria of Hy's Law in combination arm. As a second-to-market agent, this is something regulators might pay more attention to. That said, presenters mainly commented the results as meaningful confirmatory results of palbociclib, now forming the evidence of the central 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).

Beyond CDK4-6 inhibitors, another new class was under the spotlights: PARP inhibitors. However, our guess is that it will be much more the case next year as much more evidence will be available to assess their value in ovarian and in breast cancer. This is all the more true that 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 tumors (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 irrespectively of the subgroups i.e. with or without BRCA mutation although 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 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.2: Key efficacy results from the NOVA phase III trial



Source: NEJM

Highlights from day 2

Sunday clearly put immuno-oncology drugs on the forefront and a full presidential symposium was dedicated to the key publications in this category.

Anecdotally, the *Daily Reporter* which is the internal newspaper of the ESMO congress released every day put on its front page today i.e. took as the key message from yesterday's presentations the results with ipilimumab in adjuvant melanoma. This is illustrative of the central position already occupied by I.O. at ESMO while we are still at the beginning of their 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 inequities across regions and countries: “high cost is a barrier” clearly stated an Italian oncologist that was talking about I.O/I.O combinations in lung cancer. One key question remains: who should I give each drug to, how and how long? Some speakers suggested that in real life, they might decide to give some I.O drugs less long than showed in clinical trials because they act as gate-openers and their effect usually goes beyond treatment interruption.

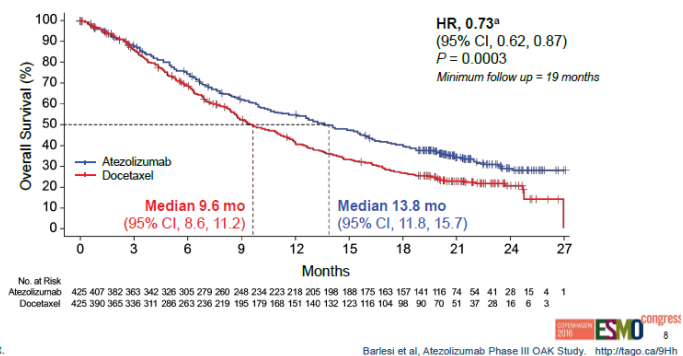
So, that said, there were several interesting presentations that overall suggested the marked influence of PD-1 and PD-L1 agents in many solid tumor types. It is worth saying that nivolumab and pembrolizumab were the more popular drugs discussed, reflecting their advance in several settings. However,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

So let’s say a few words about each of the three key presentations with the angle of learning for the European players of our coverage. From that 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 Taxotere across the board i.e. irrespectively of patient characteristics and subgroup analysis and notably between squamous and non-squamous NSCLC and between PD-L1 positive and negative (although very expressers benefited even more than others).

Curves separated early and in the end atezolizumab demonstrated median OS of 13.8 months vs 9.6 months for docetaxel (HR=0.73, p=0.0003) and this came with 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.

Fig.3: OS results from first OAK phase III data analysis

OVERALL SURVIVAL, ITT (N = 850)



Source: Roche, ESMO 2016

In conclusion, we would say that atezolizumab appears 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 across various populations obtained from one single trial with 1,225 patients and with a Q3w treatment interval (vs Q2W for nivolumab). 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 next week and with pembrolizumab’s success in 1L, is expecting to get a significant share of the 2L/3L setting with atezolizumab monotherapy while continuing to explore combinations to compete in 1L.

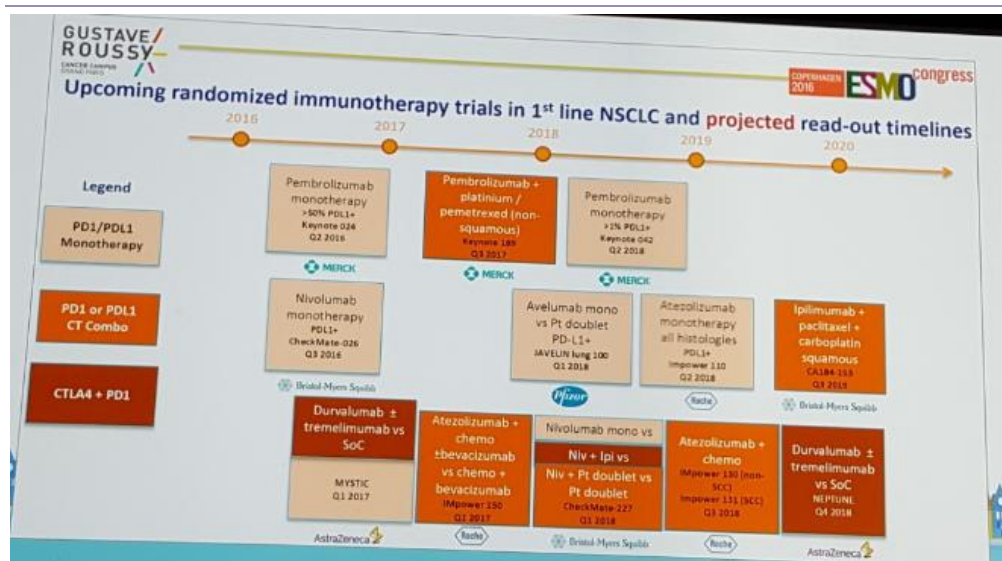
So, precisely, now moving to KEYNOTE-024 which is the study that investigated pembrolizumab against platinum-based therapies in 1L NSCLC with PD-L1 expression of 50% or more, needless to say that the results are outstanding with HR of 0.50 for median PFS and 0.60 for median OS. Overall response rate also clearly favoured pembrolizumab (45% vs 28%) with 6 complete responders and with the exception of people that never smoke (with no difference), all subgroups benefited from pembrolizumab. As with atezolizumab, safety was also in favour of the PD-1, notably grade 3-4 adverse events with an incidence of 26% (vs 51%).

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 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 to a third of NSCLC patients but once the exclusion criteria are considered (no ALK or EGFR mutation, no brain metastasis, etc...), it is only 10-15%. This is how Merck came from 1,934 patients screened down to 305 randomized patients.

So, on one hand, the results are clearly suggestive of a benefit of using I.O. 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 but the list is fairly long (see Fig.4).

Fig.4: Upcoming data with IO drugs in NSCLC



Source: ESMO 2016, JC Soria

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 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%). Some imbalances between groups (more female and more PD-L1 high expressers in the CT arm) may have participated to the failure but the magnitude of the failure suggests further investigation although. When put together with KEYNOTE-024 however, the results are suggestive of a meaningful effect of a PD-1 targeting agent only in high PD-L1 expressers and highly selected populations (like Merck did but much less so BMS). 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.

[Click here to download document](#)



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

Sector Team :
Mickael Chane Du
Hugo Solvet

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.
NEUTRAL	Opinion recommending not to trade in a stock short-term, neither as a BUYER or a SELLER, due to a specific set of factors. This view is intended to be temporary. It may reflect different situations, but in particular those where a fair value shows no significant potential or where an upcoming binary event constitutes a high-risk that is difficult to quantify. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.
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 72%

NEUTRAL ratings 0%

SELL ratings 28%

Research Disclosure Legend

1	Bryan Garnier shareholding in Issuer	Bryan Garnier & Co Limited or another company in its group (together, the "Bryan Garnier Group") has a shareholding that, individually or combined, exceeds 5% of the paid up and issued share capital of a company that is the subject of this Report (the "Issuer").	No
2	Issuer shareholding in Bryan Garnier	The Issuer has a shareholding that exceeds 5% of the paid up and issued share capital of one or more members of the Bryan Garnier Group.	No
3	Financial interest	A member of the Bryan Garnier Group holds one or more financial interests in relation to the Issuer which are significant in relation to this report	No
4	Market maker or liquidity provider	A member of the Bryan Garnier Group is a market maker or liquidity provider in the securities of the Issuer or in any related derivatives.	No
5	Lead/co-lead manager	In the past twelve months, a member of the Bryan Garnier Group has been lead manager or co-lead manager of one or more publicly disclosed offers of securities of the Issuer or in any related derivatives.	No
6	Investment banking agreement	A member of the Bryan Garnier Group is or has in the past twelve months been party to an agreement with the Issuer relating to the provision of investment banking services, or has in that period received payment or been promised payment in respect of such services.	No
7	Research agreement	A member of the Bryan Garnier Group is party to an agreement with the Issuer relating to the production of this Report.	No
8	Analyst receipt or purchase of shares in Issuer	The investment analyst or another person involved in the preparation of this Report has received or purchased shares of the Issuer prior to a public offering of those shares.	No
9	Remuneration of analyst	The remuneration of the investment analyst or other persons involved in the preparation of this Report is tied to investment banking transactions performed by the Bryan Garnier Group.	No
10	Corporate finance client	In the past twelve months a member of the Bryan Garnier Group has been remunerated for providing corporate finance services to the issuer or may expect to receive or intend to seek remuneration for corporate finance services from the Issuer in the next six months.	No
11	Analyst has short position	The investment analyst or another person involved in the preparation of this Report has a short position in the securities or derivatives of the Issuer.	No
12	Analyst has long position	The investment analyst or another person involved in the preparation of this Report has a long position in the securities or derivatives of the Issuer.	No
13	Bryan Garnier executive is an officer	A partner, director, officer, employee or agent of the Bryan Garnier Group, or a member of such person's household, is a partner, director, officer or an employee of, or adviser to, the Issuer or one of its parents or subsidiaries. The name of such person or persons is disclosed above.	No
14	Analyst disclosure	The analyst hereby certifies that neither the views expressed in the research, nor the timing of the publication of the research has been influenced by any knowledge of clients positions and that the views expressed in the report accurately reflect his/her personal views about the investment and issuer to which the report relates and that no part of his/her remuneration was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in the report.	Yes
15	Other disclosures	Other specific disclosures: Report sent to Issuer to verify factual accuracy (with the recommendation/rating, price target/spread and summary of conclusions removed).	No

A copy of the Bryan Garnier & Co Limited conflicts policy in relation to the production of research is available at www.bryangarnier.com

London	Paris	New York	Munich	New Delhi
Beaufort House	26 Avenue des Champs Elysées	750 Lexington Avenue	Widenmayerstrasse 29	The Imperial Hotel Janpath
15 St. Botolph Street	75008 Paris	New York, NY 10022	80538 Munich	New Delhi 110 001
London EC3A 7BB	Tel: +33 (0) 1 56 68 75 00	Tel: +1 (0) 212 337 7000	Germany	Tel +91 11 4132 6062
Tel: +44 (0) 207 332 2500	Fax: +33 (0) 1 56 68 75 01	Fax: +1 (0) 212 337 7002	+49 89 2422 62 11	+91 98 1111 5119
Fax: +44 (0) 207 332 2559	Regulated by the	FINRA and SIPC member		Fax +91 11 2621 9062
Authorised and regulated by the	Financial Conduct Authority (FCA) and the			Geneva
Financial Conduct Authority (FCA)	Autorité de Contrôle prudentiel et de			rue de Grenus 7
	resolution (ACPR)			CP 2113
				Genève 1, CH 1211
				Tel +4122 731 3263
				Fax+4122731 3243
				Regulated by the FINMA

Important information

This document is classified under the FCA Handbook as being investment research (independent research). Bryan Garnier & Co Limited has in place the measures and arrangements required for investment research as set out in the FCA's Conduct of Business Sourcebook.

This report is prepared by Bryan Garnier & Co Limited, registered in England Number 03034095 and its MIFID branch registered in France Number 452 605 512. Bryan Garnier & Co Limited is authorised and regulated by the Financial Conduct Authority (Firm Reference Number 178733) and is a member of the London Stock Exchange. Registered address: Beaufort House 15 St. Botolph Street, London EC3A 7BB, United Kingdom

This Report is provided for information purposes only and does not constitute an offer, or a solicitation of an offer, to buy or sell relevant securities, including securities mentioned in this Report and options, warrants or rights to or interests in any such securities. This Report is for general circulation to clients of the Firm and as such is not, and should not be construed as, investment advice or a personal recommendation. No account is taken of the investment objectives, financial situation or particular needs of any person.

The information and opinions contained in this Report have been compiled from and are based upon generally available information which the Firm believes to be reliable but the accuracy of which cannot be guaranteed. All components and estimates given are statements of the Firm, or an associated company's, opinion only and no express representation or warranty is given or should be implied from such statements. All opinions expressed in this Report are subject to change without notice. To the fullest extent permitted by law neither the Firm nor any associated company accept any liability whatsoever for any direct or consequential loss arising from the use of this Report. Information may be available to the Firm and/or associated companies which are not reflected in this Report. The Firm or an associated company may have a consulting relationship with a company which is the subject of this Report.

This Report may not be reproduced, distributed or published by you for any purpose except with the Firm's prior written permission. The Firm reserves all rights in relation to this Report.

Past performance information contained in this Report is not an indication of future performance. The information in this report has not been audited or verified by an independent party and should not be seen as an indication of returns which might be received by investors. Similarly, where projections, forecasts, targeted or illustrative returns or related statements or expressions of opinion are given ("Forward Looking Information") they should not be regarded as a guarantee, prediction or definitive statement of fact or probability. Actual events and circumstances are difficult or impossible to predict and will differ from assumptions. A number of factors, in addition to the risk factors stated in this Report, could cause actual results to differ materially from those in any Forward Looking Information.

Disclosures specific to clients in the United Kingdom

This Report has not been approved by Bryan Garnier & Co Limited for the purposes of section 21 of the Financial Services and Markets Act 2000 because it is being distributed in the United Kingdom only to persons who have been classified by Bryan Garnier & Co Limited as professional clients or eligible counterparties. Any recipient who is not such a person should return the Report to Bryan Garnier & Co Limited immediately and should not rely on it for any purposes whatsoever.

Notice to US investors

This research report (the "Report") was prepared by Bryan Garnier & Co Limited for information purposes only. The Report is intended for distribution in the United States to "Major US Institutional Investors" as defined in SEC Rule 15a-6 and may not be furnished to any other person in the United States. Each Major US Institutional Investor which receives a copy of this Report by its acceptance hereof represents and agrees that it shall not distribute or provide this Report to any other person. Any US person that desires to effect transactions in any security discussed in this Report should call or write to our US affiliated broker, Bryan Garnier Securities, LLC, 750 Lexington Avenue, New York NY 10022. Telephone: 1-212-337-7000.

This Report is based on information obtained from sources that Bryan Garnier & Co Limited believes to be reliable and, to the best of its knowledge, contains no misleading, untrue or false statements but which it has not independently verified. Neither Bryan Garnier & Co Limited and/or Bryan Garnier Securities LLC make no guarantee, representation or warranty as to its accuracy or completeness. Expressions of opinion herein are subject to change without notice. This Report is not an offer to buy or sell any security.

Bryan Garnier Securities, LLC and/or its affiliate, Bryan Garnier & Co Limited may own more than 1% of the securities of the company(ies) which is (are) the subject matter of this Report, may act as a market maker in the securities of the company(ies) discussed herein, may manage or co-manage a public offering of securities for the subject company(ies), may sell such securities to or buy them from customers on a principal basis and may also perform or seek to perform investment banking services for the company(ies).

Bryan Garnier Securities, LLC and/or Bryan Garnier & Co Limited are unaware of any actual, material conflict of interest of the research analyst who prepared this Report and are also not aware that the research analyst knew or had reason to know of any actual, material conflict of interest at the time this Report is distributed or made available.