10th October 2016

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

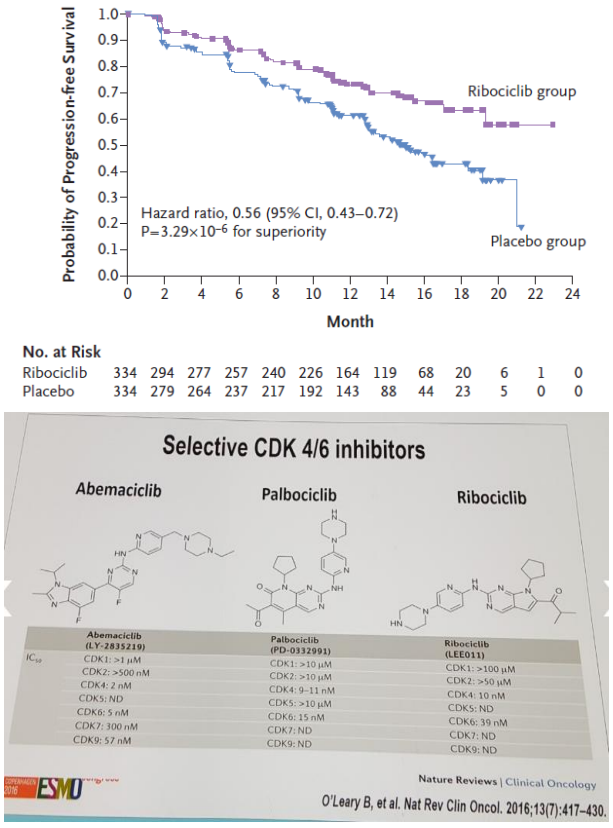
ABLYNX		**BUY**	**EUR18**
Last Price	EUR10.92	*Market Cap.*	EUR665m
ACTELION		**NEUTRAL**	**CHF180**
Last Price	CHF167.3	*Market Cap.*	*CHF18,028m*
ADOCIA		**BUY**	**EUR90**
Last Price	EUR51.99	*Market Cap.*	*EUR356m*
ASTRAZENECA		**BUY**	**5220p**
Last Price	5086p	*Market Cap.*	*GBP64,339m*
BAYER		**NEUTRAL**	**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).

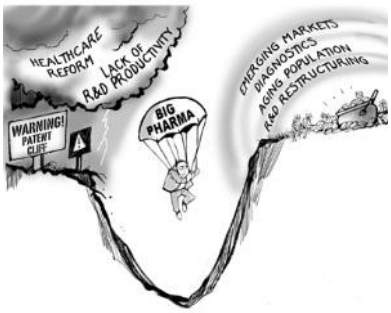
Fig.1: PFS results in MONALEESA-2 phase III trial (left) – Comparison of CDK4-6 inhibitors (right)



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*

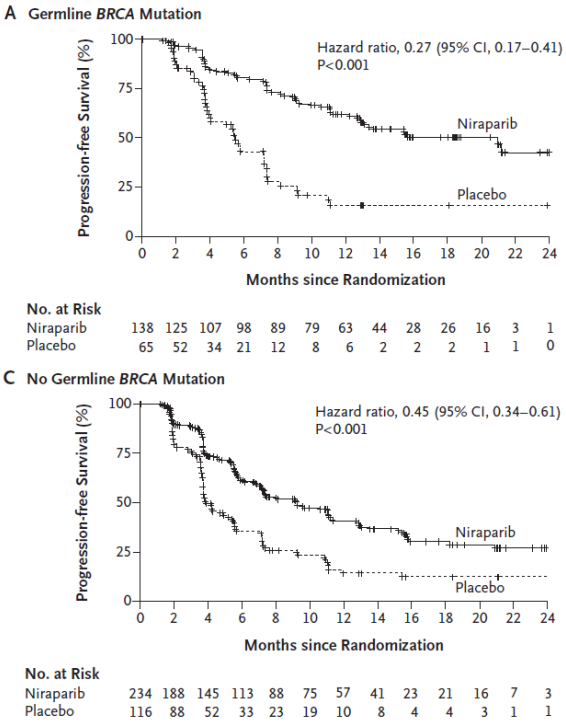


that there were 4 patients that met criteria of Hy's Law in combination arm. As a second-to-market agent, this is something regulators might pay more attention to. That said, presenters mainly commented the results as meaningful confirmatory results of palbociclib, now forming the evidence of the central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

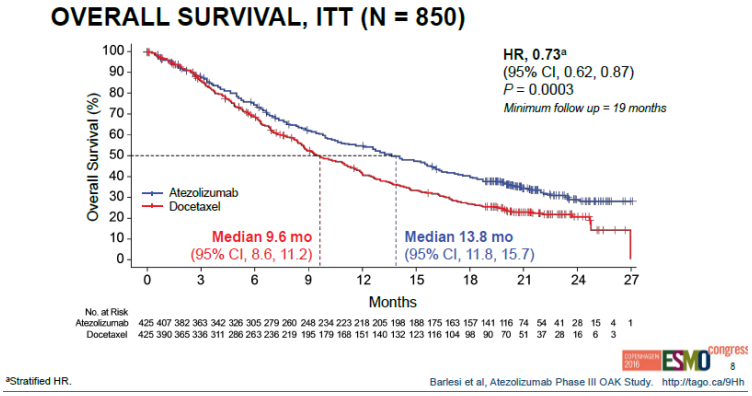
today is creating big inequities across regions and countries: “high cost is a barrier” clearly stated an Italian oncologist that was talking about I.O/I.O combinations in lung cancer. One key question remains: who should I give each drug to, how and how long? Some speakers suggested that in real life, 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



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.

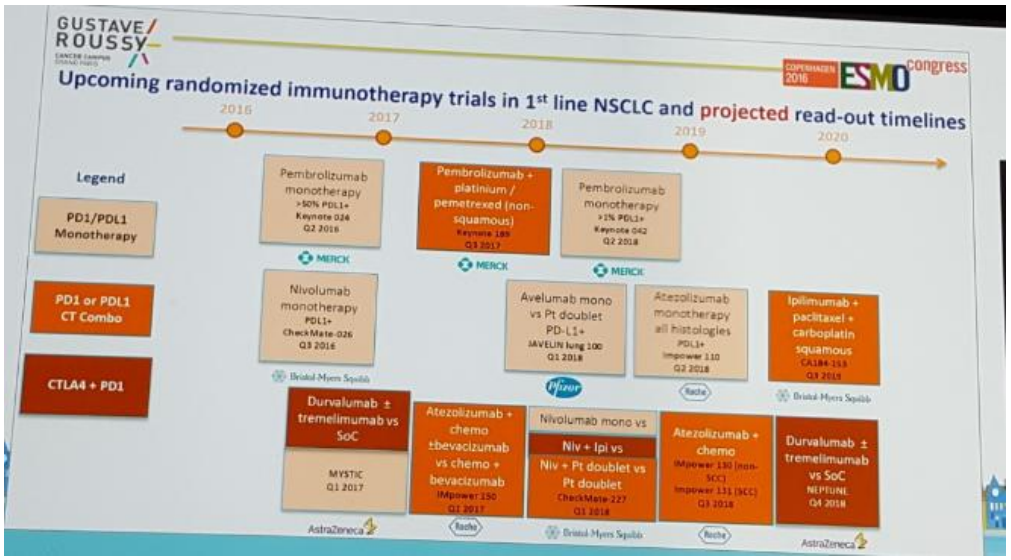
So, precisely, now moving to KEYNOTE-024 which is the study that investigated pembrolizumab against platinum-based therapies in 1L NSCLC with PD-L1 expression of 50% or more, needless to say that the results are outstanding with HR of 0.50 for median PFS and 0.60 for median OS. Overall response rate 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.

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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.

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