HILLIARD LYONS

# European Society for Medical Oncology Annual Congress – ESMO 2017

**A Review**

Analyst: Kurt A. Kemper, CFA
502-588-8446 / kkemper@hilliard.com

Institutional Sales Desk: George Moorin
502-588-9141 / gmoorin@hilliard.com

J.J.B. Hilliard, W.L. Lyons, LLC
September 13, 2017

**Note Important Disclosures on pages 6-7**
**Note Analyst Certifications on page 6**

This report is not intended to be an exhaustive summary of the European Society for Medical Oncology (ESMO) Annual Congress. Our recap is focused on our covered names, Bristol-Myers Squibb (BMY - $63.02 – Neutral) and Eli Lilly (LLY - $82.17 – Long-term Buy, $96 PT), as well as potential implications from competitors.

### *Non-Small Cell Lung Cancer (NSCLC)*

BMY provided a longer-term update to Checkmate-017 and Checkmate-057, which tested Opdivo in second-line (2L) squamous (SQ) and non-squamous (NSQ) NSCLC, respectively. Three-year overall survival (OS) rates for patients on Opdivo were 16% in CM-017 versus 6% for the comparator arm (docetaxel) and 18% versus 9% in CM-057, respectively. PD-L1 status (expression at 1% cutoff) appeared to matter for NSQ patients but not SQ patients. PD-L1 positive patients with the NSQ histology had a three-year OS of 26% versus 11% for PD-L1 negative. Both PD-L1 positive and negative patients with SQ histology had similar OS rates at 14% and 13%, respectively.

Merck (MRK - $65.46) presented updated data from cohort G of Keynote-021, which tested Opdivo rival Keytruda in combination with Lilly's Alimta and carboplatin in 1L NSQ NSCLC. The data is impressive. Progression-free survival (PFS) at 18 months occurred with 52% of patients on the combination versus only 29% of patients in the comparator arm. Median PFS was 19 months versus 8.9 months for the comparator arm. OS data is still not mature but looks strong. The median OS in the combination arm has not been reached but is a minimum of 22.8 months versus 20.9 months for the comparator. The OS hazard ratio (HR) is 0.59 (meaning a 41% reduction in risk of death), with the 95% confidence interval (CI) at 0.34 – 1.05. Because the upper range still falls over one, it could in theory still fail to prove to be statistically significant but we view that as highly unlikely given the current data.

AstraZeneca (AZN - $33.42) presented data on PACIFIC, which tested Imfinzi, a PD-L1 agent, in the adjuvant treatment of 2L Stage III unresectable NSCLC. As a reminder to investors, this is an earlier stage indication than Opdivo and Keytruda are used. The median PFS was 16.8 months versus 5.6 months for a placebo with a duration of response that has not been reached versus 13.8 months, respectively. The objective response rate (ORR) of the Imfinzi arm was 28.4% versus 16.0% for the placebo.

One presentation that may have flown under the radar was analysis of Checkmate-153. The presentation compared patients on continuous Opdivo to those on a fixed duration of one year. The continuous population had not reached median PFS versus a median PFS of 10.6 months for the one-year group with an HR of 0.45 (95% CI: 0.24 – 0.85). Median OS was directionally positive but not statistically significant; however, that could change as data matures. This analysis could have commercial implications that expand the whole market.

### *Renal Cell Carcinoma (RCC)*

Checkmate-214 was an important presentation for BMY. The trial tested the combination of Opdivo and Yervoy in 1L RCC versus the standard of care, Sutent. Median OS of all patients has not been reached for the combo versus 32.9 months for Sutent patients with an HR of 0.68; median OS for patients considered intermediate or poor risk patients also has not been reached versus 26 months for Sutent patients with an HR of 0.63. However, for good risk patients (about 25% of the trial), the combo was outright inferior to Sutent for PFS. Furthermore, in intermediate or poor risk patients, the combo failed to beat Sutent in PD-L1 negative patients in a statistically significant way for PFS, while delivering a very robust HR of 0.48 in PD-L1 positive intermediate/poor risk patients. For intermediate/poor risk patients regardless of PD-L1 status, as previously disclosed, the combo PFS was directionally positive but failed to hit statistical significance due to a high threshold. The PFS failure but clear OS success is a great example of the potential immunotherapies have to overcome PFS shortcomings as a result of strong, durable responses in the group

of patients that do respond. A final note for investors to consider about the CM-214 data is the safety profile of this dose. Only 22% of patients in the combo discontinued treatment as a result of adverse events versus 31% in Checkmate-067, a trial testing the combo in 1L melanoma. CM-214 used more Opdivo and less Yervoy in the first four doses than CM-067.

Exelixis (EXEL - $26.95) and partner Ipsen (IPSEY - $35.00) announced updated data from the Phase 2 CABOSUN trial testing Cometriq (cabozantinib) in 1L RCC intermediate/poor risk patients only. The PFS was 8.6 months for Cometriq versus 5.3 for Sutent. The PFS HR was 0.48 (95% CI 0.31 – 0.74). It appears CABOSUN pulled in sicker patients given the weak Sutent performance, so we would focus on the HR, but we would also point out CABOSUN was a much smaller trial. OS was directionally positive: 26.6 months for Cometriq versus 21.2 months for Sutent but not statistically significant with an HR of 0.80 (95% CI 0.53 – 1.21). ORR was 20% for Cometriq versus 9% for Sutent. The discontinuation rate due to adverse events was 21% in Cometriq and 22% in Sutent.

Merck presented data of a Phase 1b/2 trial testing Keytruda and Eisai's (ESALF - $51.36) Lenvima in both 1L and 2L RCC. The ORR was 63% with a disease control rate (DCR, which includes patients with stable disease) of 96%. The median PFS had not been reached at a follow up of 9.7 months. In 1L patients only, the ORR was 83% with a DCR of 100%. This is very strong data but we urge caution in excitement as only 30 patients (12 in 1L) were in the trial.

### *Gastric, Gastroesophageal, or Esophageal*

Merck presented updated data from Phase 2 Keynote-059, testing Keytruda as a monotherapy or in combination with chemotherapy in multiple lines of therapy, although investors will be most interested in 1L data. Keytruda mono generated an ORR of 26% in PD-L1 positive patients versus 69% for the combo. In PD-L1 negative patients, the combo generated an ORR of 38%. In all patients, the combo generated a PFS of 6.6 months versus the monotherapy PFS of 3.3 months. The six-month OS rate for the combo was 76% versus 72.9% for monotherapy. In the combo cohort, safety data remained the same as the last update: serious adverse events occurred in 76% of patients, but only 12% led to discontinuation. The data is strong but based on two arms of 25 patients (combo) and 31 (mono).

### *Urothelial (Bladder) Cancer*

LLY presented the RANGE data, which tested Cyramza in combination with docetaxel in the 2L setting. PFS for the combo hit 4.1 months versus the comparator arm (docetaxel alone) PFS of 2.8 months with an HR of 0.78 (95% CI: 0.61 – 0.94). The ORR was 24.5% for the combo versus 14.0% for the comparator. OS data is not mature yet. This is strong data that we believe will boost market share for Cyramza in the indication. Importantly, the trial included patients with checkpoint inhibitors (such as Opdivo), so this market is unlikely to shrink. Lilly stated results for those on previous checkpoint inhibitors were similar to the overall trial, although numbers were small.

Merck presented follow-up data for Keynote-045, which tested Keytruda in 2L treatment. The median OS was 10.3 months versus 7.4 months for the comparator arm. The HR was 0.70 (95% CI: 0.57 – 0.86). The one year OS was 44% for Keytruda and 31% of the comparator; 7% of Keytruda patients experienced a complete response (CR).

### *Melanoma*

BMY presented Checkmate-238, which tested Opdivo versus its own Yervoy in the adjuvant treatment of melanoma. Median recurrence-free survival (RFS) has not been reached for either group yet, but the 18-month RFS rate for Opdivo was 66.4% versus Yervoy's 52.7% with an HR currently at 0.65 (95% CI: 0.51 – 0.83).

BMY also presented more data on relatlimab, the anti-LAG-3 antibody. Relatlimab appears to have promise in the LAG-3 positive population with solid safety data.

Merck and Incyte (INCY - $123.15) presented updated ECHO-202/ Keynote-037 data for the Keytruda/ epacadostat combo in multiple lines of therapy. In all patients, the ORR was 56% with an impressive 14% CR rate. The median PFS was 12.4 months but notably 22.8 months in 1L patients. The combo was tolerable as well: only 20% of patients experienced serious adverse events with only 6% discontinuing treatment.

Finally, Idera Pharmaceuticals (IDRA - $2.055) presented some intriguing but far-too-early-to-get-excited-about data about its IMO-2125 molecule combined with Yervoy in melanoma patients who failed PD-1 therapy. In a small Phase 1 trial, the dose Idera plans to advance to the next phase, in combination with Yervoy, generated a DCR of 67%.

### *Head and Neck Cancer*

Merck unveiled brand new data from Checkmate-040, just missing OS statistical significance in 2L squamous cell carcinoma of the head and neck (SCCHN). The median OS for Keytruda patients was 8.4 months versus 7.1 months for the comparator with an HR of 0.81 (95% CI: 0.66 – 0.99). However, the p-value of 0.0204 did not meet the pre-specified p-value of 0.0175. Additional analysis by PD-L1 status tells more of a story. Patients with any PD-L1 expression experienced a 25% reduction in risk of death and patients with PD-L1 expression over 50% experienced a 46% reduction in risk of death.

### *Breast Cancer*

MONARCH-3 was the main draw in breast cancer, in our opinion. The trial tested its abemaciclib in combination with endocrine therapy in 1L HR+/HER2- patients. The efficacy data is strong. The median PFS has not been reached with an HR of 0.54 (95% CI: 0.41 – 0.72). The ORR was 59% versus only 44% in the comparator arm. Of course, investors were hoping for better efficacy data versus Pfizer's (PFE - $35.37) Ibrance, which returned a PFS HR of 0.58 (95% CI: 0.46 – 0.72) in the PALOMA-2 trial. While MONARCH-3 data is still maturing and abemaciclib could appear marginally more efficacious, we don't believe the marketplace will view it as a superior molecule.

The differentiator for abemaciclib and Ibrance comes from safety. Abemaciclib caused diarrhea in 81% of patients in the trial (actually lower than previous trials), but only 9.5% of diarrhea cases were considered serious. Abemaciclib caused neutropenia in 41.3% of patients (serious cases: 21.1%). Ibrance, in comparison generated far less diarrhea (26.1% total, 1.4% serious) but significantly more neutropenia (79.5% total, 66.5% serious). An additional concern of venous thromboembolism (VTE) cropped up for abemaciclib, with 4.9% of patients.

### *Concluding Thoughts*

**NSCLC:** Merck continues to raise the bar in 1L NSCLC and put pressure on Checkmate-227 results. We would like to remind investors BMY has diversified its approach to 1L NSCLC, and we think this plays in their favor both in the short-term for the multiple options they will be presenting to physicians and payers, as well as the long-term as the market continues to fragment based on either current or undiscovered biomarkers. AZN's PACIFIC trial suggests the entire immunotherapy market could be larger than originally anticipated, treating earlier stages of cancer, but the data is young and more progress may be needed for patients that don't respond to immunotherapy before the marketplace accepts it. Some physicians have voiced concern earlier-stage use of immunotherapy agents could take away options if the cancer progresses or returns.

**RCC:** While the CM-214 news prior to the start of ESMO presented investors with a positive catalyst, ESMO itself was more nuanced for BMY in RCC, in our opinion. We think the Opdivo/ Yervoy combo becomes the clear standard of care in intermediate/poor risk PD-L1 positive patients. However, in intermediate/poor risk PD-L1 negative patients, we think BMY will initially share some of the market with Exelixis; if Exelixis OS data matures to be statistically significant, we think Exelixis takes most of the market in PD-L1 negative patients. Additionally, although still early, combination data from several rivals at both ASCO and ESMO this year suggests RCC will be a highly competitive market, even if BMY and Exelixis have an early lead.

**Melanoma:** Just as this indication was the first frontier for immunotherapy, it looks to be the first frontier for patients whose cancer progresses after immunotherapy. Additionally, the Merck-Incyte combo should give BMY investors some pause, but we wouldn't be too concerned yet. An efficacy difference is far from clear, but we will concede the competition's combo appears more tolerable than the Opdivo/ Yervoy combo.

**Breast:** The breast cancer data was solid for Lilly, in our opinion. As expected, physicians and patients will have to choose between the side effect of either diarrhea with abemaciclib or neutropenia with Ibrance or Novartis' (NVS - $85.72) Kisqali while expecting similar efficacy. Lilly has been quick to point out diarrhea occurs early in the treatment and typically is resolved with over-the-counter medications. Lilly has also pointed out the strength of abemaciclib in poor prognosis patients, such as those without bone-only disease or those with liver metastases. The latter generated an impressive HR of 0.49 and the former had an HR of 0.51 versus Ibrance's 0.65 (95% CI: 0.51 – 0.84). We think Lilly could carve out a strong market share in this niche. On the other hand, patients at risk of blood clotting could be pushed away from abemaciclib; we believe the VTE data hurts abemaciclib only marginally.

As of earlier this year, Pfizer's Ibrance – prior to the launch of Kisqali – had 45% of the addressable market in the U.S. only. Pfizer is still in the process of launching in other major markets. Thus, there is clear opportunity for growth for abemaciclib and we think the molecule can take some market share in poor prognosis patients. Having said that, trading one side effect for another won't necessarily allow Lilly to steal a tremendous amount of market share, in our opinion.

This marks yet another significant oncology conference that should leave investors and patients alike enthralled with the progress in the field. ESMO 2017 sticks out to us for the potential advances being made for patients not responding to immunotherapies.

## Analyst Certification

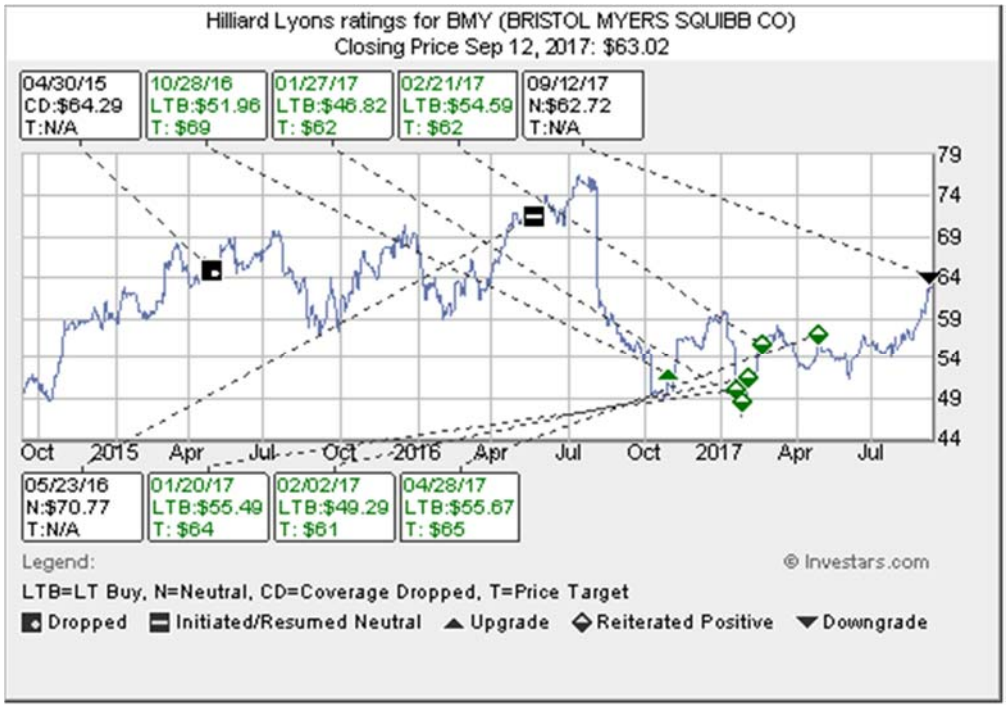
I, Kurt A. Kemper, CFA, hereby certify that the views expressed in this research report accurately reflect my personal views about the subject company(ies) and its (their) securities. I also certify that I have not been, am not, and will not be receiving direct or indirect compensation in exchange for expressing the specific recommendation(s) in this report.

## Important Disclosures

Hilliard Lyons' analysts receive bonus compensation based on Hilliard Lyons' profitability. They do not receive direct payments from investment banking activity.

**Investment Ratings:**
**Buy** - We believe the stock has significant total return potential in the coming 12 months.
**Long-term Buy** - We believe the stock is an above average holding in its sector, and expect solid returns to be realized over a longer time frame than our Buy rated issues, typically 2-3 years.
**Neutral** - We believe the stock is an average holding in its sector, is currently fully valued, and may be used as a source of funds if better opportunities arise.
**Underperform** - We believe the stock is vulnerable to a price set back in the next 12 months.

**Definitions of Suitabilities:**
**1.** A large cap, core holding with a solid history.
**2.** A historically secure company which could be cyclical, has a shorter history than a "1" or is subject to event driven setbacks.
**3.** An above average risk/reward ratio could be due to small size, lack of product diversity, sporadic earnings or high leverage.
**4**. Speculative, due to small size, inconsistent profitability, erratic revenue, volatility, low trading volume or a narrow customer or product base.




| | Hilliard Lyons Recommended Issues | | Investment Banking Provided in Past 12 Mo. | |
|---|---|---|---|---|
| Rating | # of Stocks Covered | % of Stocks Covered | Banking | No Banking |
| **Buy** | 40 | 32% | 10% | 90% |
| **Hold/Neutral** | 77 | 62% | 8% | 92% |
| **Sell** | 8 | 6% | 0% | 100% |

*As of 6 September 2017*

## Other Disclosures

Opinions expressed are subject to change without notice and do not take into account the particular investment objectives, financial situation or needs of individual investors. Employees of J.J.B. Hilliard, W.L. Lyons, LLC or its affiliates may, at times, release written or oral commentary, technical analysis or trading strategies that differ from the opinions expressed here.

J.J.B. Hilliard, W.L. Lyons, LLC is a multi-disciplined financial services firm that regularly seeks investment banking assignments and compensation from issuers for services including, but not limited to, acting as an underwriter in an offering or financial advisor in a merger or acquisition, or serving as placement agent in private transactions.

The information herein has been obtained from sources we believe to be reliable but is not guaranteed and does not purport to be a complete statement of all material factors. This is for informational purposes and is not a solicitation of orders to purchase or sell securities. 