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R&D Matters – The Five Top Research & Development Stories of 2016

by Alex Shimmings

If you take the temperature of R&D productivity you get a good indicator of the health of the pharma and biotech industries, making new drug development stories a perennial favourite with *Scrip* readers. Here we take a look at the five biggest R&D stories this year.

The top R&D story of the year, in the eyes of *Scrip* readers, was the disaster that befell Portuguese company *Bial-Portela & CA SA* when one volunteer died and several others were hospitalized during a Phase I trial of its novel inhibitor of FAAH – known as BIA 10-2474 – for various neurological conditions. Indeed, this was one of the top stories of the year, and is detailed in the companion piece *2016 – The Pharma Year In Review*. But failures in other trials provided the more usual drug development tragedies for other companies and, by extension, the patients who lost a potential life-saving treatment option.

Keytruda To Opdivo: 'Checkmate'

Chief among these was the surprise failure of *Bristol-Myers Squibb Co.*'s PD-1 inhibitor *Opdivo* in the much-anticipated CheckMate 026 study in first-line lung cancer.

The behemoth of the checkpoint inhibitor world missed the primary progression-free-survival endpoint in the trial, taking everyone by surprise and prompting a 16% dive in the company's share price on Aug. 5. Analysts didn't hold back: "clear disappointment and overall surprise", the "worst-case scenario" and "possibly the biggest surprise of my career" were just some of their responses.

2016 – The Pharma Year In Review

By Alex Shimmings

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As we enter a new year, *Scrip* takes a look at the five biggest themes that got the most hits from our readers over the last 12 months.

Read the full article here

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Just a week earlier, at BMS's second quarter results call, the company had boasted an 80% market share for its product with $840m in sales from a range of licensed indications, including melanoma, second-line NSCLC, renal cell cancer, and Hodgkin's lymphoma. Back then, progress into first-line NSCLC was seen as the obvious next step to total market dominance and further riches.

Lung cancer is the largest market for the cancer immunotherapies and BMS had already built a strong lead over rival *Merck & Co. Inc.*'s *Keytruda* (pembrolizumab) in the second-line NSCLC setting, but the first-line setting is the jewel in the NSCLC crown.

In an attempt to catch up, Merck had been pushing Keytruda hard in first-line NSCLC and won an early victory in July when it became first to report data from a first-line lung cancer trial showing that Keytruda improved PFS and also overall survival in the first-line KEYNOTE 024 study. Its victory became complete in October when it sailed to early approval at the US FDA for this patient population, while the presentation of the full CheckMate 026 results at ESMO showed just how badly Opdivo had fared: it performed worse than the control. The data did not even provide BMS with a crumb of comfort of a trend towards an efficacy benefit in patients with greater than 50% PD-L1 expression, which some had hoped for.

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'Total Disaster' In First-Line Lung Cancer For BMS's Opdivo

Merck's Keytruda Chemo-Combo Data Has Big Implications For Future Of Immuno-Oncology

PD-1 Deep Dive: Lung Cancer Market Braced For Change

Bristol Still Rules Immuno-Oncology, But For How Long?

It's Here: Merck's Keytruda Cleared For First-Line Lung Cancer

To rub salt into the wound, at the same meeting Merck presented the first positive Phase II data from the KEYNOTE-021 study that suggest the combination of Keytruda with chemotherapy could become a new standard for treating first-line NSCLC patients who test negative for PD-L1, as well as being an option for some PD-L1 positive NSCLC patients.

In short, studies reported this year have precipitated a period of rapid change for the NSCLC market that is expected to last for several years as the arrival of *Roche*'s PD-L1 inhibitor *Tecentriq* (atezolizumab) shakes up the market for second-line NSCLC patients and clinical data from other combinations start to read out.

No PCSK9 Pill, No Bococizumab

Pfizer Inc.'s decision not to move forward with the development of an oral PCSK9 inhibitor for the treatment of high cholesterol was another huge hit with readers.

In August, President-Worldwide R&D Mikael Dolsten revealed the company's fears during the company's second-quarter sales and earnings that the product's efficacy just wouldn't stand up to its the injectable rivals, *Amgen Inc.*'s *Repatha* (evolocumab) and *Sanofi*/*Regeneron Pharmaceuticals Inc.*'s *Praluent* (alirocumab).

An oral pill would have had an interesting competitive position versus the injectable products, though its development was years off and the market dynamics for the PCSK9 blockers that have launched have so far been challenging, driven largely by payer pushback on price. The injectables cost roughly $14,000 a year.

The disappointment was compounded later in the year when Pfizer terminated late-stage development of its lead injectable PCSK9 inhibitor bococizumab. Pfizer said the decision was based on updated data from six Phase III trials testing bococizumab, including two studies testing the drug out to 52 weeks, which led the company to change its mind about the commercial potential of the lipid-lowering drug. The 52-week data showed an "unanticipated attenuation of low-density lipoprotein cholesterol (LDL-C) lowering over time, as well as a higher level of immunogenicity and higher rate of injection-site reactions with bococizumab than shown with the other agents in this class."

Pfizer had been hoping to get bococizumab to market shortly after its rivals released cardiovascular outcomes data on Repatha and Praluent – it is hoped CVOT data will expand the market for the cholesterol-lowering drugs which have struggled amid pricing controversies.

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Pfizer Dashes Hopes For A PCSK9 Pill

Pfizer's Bococizumab Discontinuation Increases Uncertainty For Other PCSK9s

Analysts pointed towards issues with anti-drug antibodies against bococizumab as being the likeliest culprit for the drug's waning effects against LDL-C, something which does not seem to be affecting the older products. The loss of their nearest competitor now leaves these poised to reap the benefits of any success in their outcomes studies, due early 2017.

It also leaves Pfizer's CV pipeline all the poorer, although CEO Ian Read did say the company would continue to look for ways to strengthen its position in the field. How long and hard this search will be remains to be seen, however, with other pipeline areas like oncology and inflammation/immunology growing increasingly large.

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Sola And Thanks For The Memories

Next of the list was the failure of *Eli Lilly & Co.*'s Alzheimer's anti-amyloid disease candidate, solanezumab, in the EXPEDITION3 study in November. The result may have been largely expected but it was still a disappointment for the field which has had little cause for cheer.

Sola's two previous Phase III trials EXPEDITION and EXPEDITION2 both failed but a pre-specified pooled analysis showed a statistically significant improvement in patients with mild disease, keeping hope for the product alive. In a final punt, Lilly decided to test the product in patients earlier in the course of their disease, and confirming the presence of amyloid pathology via PET screening or cerebrospinal fluid testing.

But still EXPEDITION3 did not meet the primary endpoint, a statistically significant slowing in cognitive decline among people with mild dementia due to Alzheimer's disease as measured by the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog).

In the end, the results, including many secondary clinical endpoints, favored solanezumab, but the magnitudes of treatment differences were small, Lilly said. It was not enough, and the company confirmed that it would not pursue a regulatory submission for solanezumab.

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Lilly's Solanezumab Fails, But The Surprise Would Have Been Success

After Solanezumab, What's Next? Alzheimer's Options Take The Stage At CTAD

Lilly's Alzheimer's EXPEDITION3 Proves Positive For Biogen's Anti-Amyloid At CTAD

But the game is not yet over for the amyloid hypothesis. The weak signal in the EXPEDITION3 and its sister studies still suggest a role for amyloid and are seen as positive for *Biogen Inc.*'s earlier-stage amyloid-clearing antibody product aducanumab – this product has a slightly different mechanism and caused a splash at the Clinical Trials in Alzheimer's Disease (CTAD) conference in San Diego in December.

CAR-T To Market

Unsurprisingly, given the dominance of immune-oncology in the minds of R&D executives, the fortunes of the CAR-T products held the attention of readers in 2016.

In a year of changing fortunes for key players, *Novartis AG* and *Kite Pharma Inc.* are now vying for pole position in the race to market the first chimeric antigen receptor T-cell product after pioneer *Juno Therapeutics Inc.*'s most advanced CD19-targeting CAR-T therapy, JCAR015, was stymied by fatal cerebral edemas which resulted in the on, off, on-again clinical hold of its

leading program, the Phase II ROCKET trial in acute lymphoblastic leukemia (ALL).

Juno's initial position was that the deaths were caused by the use of fludarabine in a preconditioning cyclophosphamide chemotherapy regimen and the agency lifted a July hold on research after the company revised the protocol to stop using that agent. But fatal edema continued, even though the company insisted the removal of the chemotherapy did reduce the treatment's toxicity, and a voluntary hold was put on the study in November.

In early December, Novartis and Kite revealed their plans to file BLA submissions at the FDA in early 2017 based on data presented during the American Society for Hematology (ASH) meeting in San Diego, for their products, CTL019 and KTE-C19. Both consist of each treated patient's own T-cells reengineered to express CD19 so that the T-cells will attack cancer cells expressing the antigen and both have breakthrough therapy designations which could see them reach the market by the end of 2017.

Kite said it has initiated a rolling BLA submission that the company will complete by the end of the first quarter of 2017 for KTE-C19 in relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL) patients ineligible for autologous stem cell transplant. Kite reported positive interim data from the Phase II portion of its Phase I/II clinical trial ZUMA-1 in September.

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Novartis, Kite Neck-And-Neck In CAR-T Race; Deaths Keep Juno In Third Place

New Interim CAR-T Data Support Kite's BLA Submission Plans

Juno Stresses Differences Between Its CAR-Ts As ICAR015 Trial Put On Hold Again

Juno ROCKETs On Fast Clinical Hold Resolution

Three Deaths In Trial Mean Clinical Hold For Juno's Lead CAR-T Therapy

ASH Ends With Consistent Kite CAR-T Data, Some Hope For Juno

Novartis meanwhile plans a BLA filing in early 2017 and will seek EU approval later in the year for CTL019 in the treatment of relapsed and refractory pediatric and young adult patients with B-cell ALL based on data from the global Phase II ELIANA clinical trial. Presented at ASH on Dec. 3., this showed that 82% of patients – 41 out of 50 children and young adults – achieved complete remission or complete remission with incomplete blood count recovery three months after infusion of the Novartis cell therapy with no minimal residual disease detected. The relapse-free rate among the responders was 60% six months after infusion.

Progress For Migraine

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After all the bad R&D news, readers were keen to hear news of clinical trial success for a new class of treatments for migraine, the CGRP inhibitors, and the epic battle to market shaping up between the major players. The jury is still out on which of the four products in late-stage development looks best-placed to succeed on the market, making speed at the regulators of the essence.

The first to report Phase III data was Amgen and Novartis's biologic erenumab (AMG 334) from the ARISE study in episodic headache patients in September. But on their tail are *Alder BioPharmaceuticals Inc.*, Eli Lilly & Co. and *Teva Pharmaceutical Industries Ltd.*, each with a monoclonal antibody in Phase III development that has shown impressive – and impressively similar – results in mid-stage clinical trials.

A second positive trial for erenumab reported in November in the STRIVE study in episodic migraine is keeping Amgen and Novartis on track to be first to file in 2017 – a timing advantage which could prove vital in a sea of very similar competitors. Analysts expect the products' respective side-effect profiles to come into play as each tries to differentiate itself against the others, and against the next wave of oral and intranasal CGRP products coming through the pipeline, particularly from Allergan.

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Amgen Plans 2017 Filings After Second Phase III CGRP Inhibitor Success

Speed Is Everything In CGRP Race As Amgen/Novartis Reveal Phase III Data

Allergan's Oral Drugs Overlooked In CGRP Inhibitor Development Race

Alder Readies To Take On Teva, Others In Migraine

There are no products yet approved specifically for the prevention of migraine, and patients with episodic migraines spend about 14 days each month with a debilitating headache. Increased levels of CGRP – or calcitonin gene-related peptide – have been reported in patients with migraine, making it a novel target for the disease.