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Surprise! It's A Phase III Failure

by Jessica Merrill

When Phase III clinical trial failures happen it is a painful blow – to the drug manufacturer, to investors and to patients. *Scrip* takes a look at some of the biggest Phase III surprises since 2010.

When *Bristol-Myers Squibb Co.* announced Aug. 5 that a key Phase III trial testing the checkpoint inhibitor *Opdivo* (nivolumab) in first-line lung cancer, CheckMate 026, missed the primary progression-free survival endpoint, the news hit the company like a ton of bricks.

Given Bristol's leading position in cancer immunotherapy, its massive R&D investment and meticulous development of Opdivo and fellow checkpoint inhibitor *Yervoy* (ipilimumab) until that point, almost anyone following the space would have bet on Bristol notching another success, especially investors.

The news led Evercore ISI analyst Mark Schoenebaum to declare, "This is a major surprise – possibly the biggest clinical surprise of my career." (Also see "*Does CheckMate 026 Take Bristol Out Of The End Game?*" - Scrip, 5 Aug, 2016.)

That got the *Scrip* team thinking about the times we've been surprised. There have been many, many late-stage clinical trial failures in the last decade. As any savvy life sciences investor knows, the only guarantee when it comes to drug development, is there is no guarantee, even in the final phase.

But some Phase III failures truly stun, whether because of the hype around the drug, the level of R&D investment, the confidence of management and investors, the timing (shortly after a multibillion-dollar deal was announced, for example) or because of industry's sometimes incredible refusal to give up when it should.

Not every late-stage failure means the drug is a failure, as is certainly the case with Opdivo, which is already a commercial success and may still have an opportunity in first-line lung cancer, depending on biomarker data. Bristol took a gamble with the way it ran the trial, enrolling a

broader set of patients by PD-1 status than *Merck & Co. Inc.* did with its rival drug *Keytruda* (pembrolizumab) and the bet didn't pay off. (Also see "*Opdivo Fallout: Rivalry In PD-1 Market To Continue, More Trials Could Mean More Failures*" - Scrip, 11 Aug, 2016.)

Here are 10 other Phase III bets since 2010 that crashed and burned – and surprised everyone watching along the way.

Pharma Flops: 10 Of Industry's Most Surprising Phase III Trial Failures

- Pfizer Inc./Medivation Inc.'s dimebon: In March 2010, two Phase III clinical trials failed to show improvements on either of two primary endpoints – measures of cognition and global function – in Alzheimer's patients. Dimebon had showed strong efficacy in a Phase II/III trial and enthusiasm was running high that dimebon could be the first disease-modifying drug to reach the market for Alzheimer's. As it turned out, dimebon was a bomb. Six years and many more late-stage Alzheimer's trial failures later, industry is still hoping to score on the disease-modifying front. (Also see "*Prospects For Pfizer/Medivation's Dimebon Dashed By Phase III Flop*" - Pink Sheet, 3 Mar, 2010.)
- Sanofi's iniparib: A Phase II trial showed improved survival in women with triple-negative breast cancer treated with the PARP inhibitor, so investors were stunned when the Phase III trial did not deliver on the progression-free survival or overall survival endpoints in January 2011. Another trial in lung cancer failed in 2013, and the company took a $285m impairment charge related to its decision to end development of iniparib. (Also see "*Sanofi Oncology's Transformation Rests On Fedratinib, At Least In The Near-Term*" - Pink Sheet, 26 Aug, 2013.) AstraZeneca, on the other hand, rebounded from a Phase II failure of its PARP inhibitor *Lynparza* (olaparib) in 2011 with success in BRCA-positive patients. (Also see "*AstraZeneca's Olaparib Clears FDA For Later Therapy Line In Ovarian Cancer*" - Pink Sheet, 19 Dec, 2014.)
- AstraZeneca PLC/Targacept Inc.'s TC-5214: AstraZeneca bought into Targacept's novel neuronal nicotinic receptor antagonist TC-5214, paying $200m upfront with the promise of $1.24bn in milestone fees (high for central nervous system drugs at the time) in 2009 to develop the drug for major depressive disorder. The company moved aggressively with the development plan, initiating four Phase III clinical studies, so when the first study failed to show efficacy in November 2011, it was a big surprise. The others all eventually failed too and the companies decided not to file for approval – no surprise to investors by the time the end was announced. (Also see "*AstraZeneca dumps Targacept's antidepressant TC-5214 after two more Ph III failures*" - Scrip, 20 Mar, 2012.)
- Reata Pharmaceuticals Inc./Abbott Laboratories Inc.'s bardoxolone: The partners thought they had a future blockbuster on their hands when a Phase III program testing bardoxolone in chronic kidney disease was terminated suddenly in October 2012 due to an increased risk of mortality. Abbott had paid a handsome $400m upfront in 2009 for ex-US rights to the first-in-class antioxidant inflammation modulator that activates the Nrf2 pathway and was

just in the process of spinning out its pharmaceutical business into a new company called *AbbVie Inc.* (Also see "*Bardoxolone Blow-Up: Reata/Abbott CKD Drug Halted In Phase III*" - Pink Sheet, 18 Oct, 2012.)

- Eli Lilly & Co.'s solanezumab: Lilly was so invested and enthusiastic about the opportunity for developing a disease-modifying treatment for Alzheimer's disease that investors couldn't help but hope for a positive outcome for the anti-beta amyloid drug solanezumab despite the obvious risks. When Lilly announced the Phase III studies failed in August 2012 the pain was still real. Perhaps the bigger surprise was that Lilly decided to move forward with a third Phase III trial in mild Alzheimer's patients, based on a pooled analysis of the two earlier studies. Investors are still awaiting the results of that trial. This time the outcome may be a surprise too – a positive one. (Also see "*Four years late, 50% success rate, Lilly's solanezumab stays in PhIII*" - Scrip, 13 Dec, 2012.)
- GlaxoSmithKline PLC's darapladib: It's hard to resist the temptation of upside, such as the potential for drugs like the Lp-PLA2 inhibitor darapladib in chronic coronary heart disease, where the commercial opportunity is so large it's hard to see the warning signs. GSK made a big investment in a 15,828-patient cardiovascular outcomes trial, which failed to reduce CV events among the trial's patients in November 2013. (Also see "*GSK's Darapladib Poised To Become Latest Cardiovascular Outcomes Casualty*" - Pink Sheet, 12 Nov, 2013.) But GSK has plenty of company in losing money on cardiovascular outcomes trials, including...
- Merck & Co. Inc.'s *Tredaptive*: The results of Merck's HPS2-THRIVE trial testing the niacin/laropiprant combination pill in patients with high cholesterol led the company to end development of the drug in the US and threw cold water on the hypothesis that increasing HDL cholesterol, the so-called good cholesterol, could improve cardiovascular outcomes for patients. The results of the enormous trial, which enrolled some 25,000 patients, were announced in January 2013. (Also see "*Another Low Blow For Raising HDL; Merck's Tredaptive Fails Phase III Trial*" - Pink Sheet, 23 Jan, 2013.)
- Merck/Endocyte Inc.'s vintafolide: Vintafolide had already won conditional marketing approval in the EU based on positive progression-free survival in a subset of ovarian cancer patients when the Phase III PROCEED study was halted early due to futility. Given the momentum around the drug conjugate that had investors cheering, Endocyte's stock dropped 60% on the news and it hasn't recovered. (Also see "*Merck/Endocyte Mulling Vintafolide's Future After Failure In Ovarian Cancer*" - Pink Sheet, 2 May, 2014.)
- AstraZeneca/Amgen's brodalumab: Investors expected the IL-17 blocker brodalumab would be a mega-blockbuster for psoriasis and stand up to rivals like Novartis' *Cosentyx* already on the market. But while the Phase III studies, released in March 2015, showed good efficacy versus an active comparator, they also showed an increase in suicidal ideation. Amgen bowed out immediately and AstraZeneca eventually managed to out-license the drug to *Valeant Pharmaceuticals International Inc.*, which is hoping to secure FDA approval soon. The big surprise will be if it finds a commercial market competing against rivals that don't carry the

same risk. (Also see "*Amgen dumps brodalumab; AstraZeneca losing a blockbuster?*" - Scrip, 22 May, 2015.)

- Eli Lilly's evacetrapib: It seems like it would have been hard to be surprised when Lilly announced it would stop a Phase III trial testing its cholesteryl ester transfer protein (CETP) inhibitor in patients with high cholesterol due to futility in October 2015, after Pfizer's torcetrapib failed in 2006 and Roche terminated dalcetrapib for lack of efficacy 2012, but let's chalk this one up to the entire class being a disappointment and industry's refusal to stop throwing millions of dollars at drug targets when they probably should. That, at least, continues to surprise. (Also see "*Who Suffers From Lilly's Evacetrapib Failure?*" - Scrip, 12 Oct, 2015.)

(Editor's note: this story was updated to reflect that Lilly's ongoing Alzheimer's study for solanezumab is in patients with mild disease, not moderate).