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The (Non-COVID) Clinical Trial Hits And Misses Of 2020

by Alex Shimmings

Putting aside the coronavirus pandemic for a while, and turning to industry's more bread and butter R&D activities, *Scrip* takes a look at the industry's biggest clinical trial hits and misses of the year.

MISSES

No one wants a Phase III failure but they are a sad fact of pharma life, and sometimes even a disaster. Here are five of the more painful disappointments met with in 2020.

Unhappy New Year For Incyte With Itacitinib Flop

Incyte Corporation's hopes of reducing its reliance on Jakafi (ruxolitinib) suffered a blow after a Phase III trial of its selective JAK1 inhibitor itacitinib failed in January, raising concerns about the company's ability to generate value from its hefty R&D investments.

The Phase III GRAVITAS-301 study evaluating itacitinib in combination with corticosteroids in patients with treatment-naive acute graft-versus-host disease (GVHD) did not meet the primary endpoint of improving overall response rate at day 28 compared with placebo plus corticosteroids (74.0% vs 66.4%, respectively). Also, there was no difference observed in non-relapse mortality after six months, the study's key secondary endpoint, between the treatment and placebo arms.

Incyte cited a higher than anticipated response rate for the placebo/steroids arm as a likely

reason for the negative results.

The product is still in the Phase III GRAVITAS-309 trial for steroid-naive chronic GVHD in another study, but some observers said expectations for success were low given the complexity of the disease combined with the Phase III fail.

Credit Suisse analysts said that following positive Phase I data and approval of the flagship JAK inhibitor Jakafi in steroid-refractory acute GVHD in May last year, "the negative result of GRAVITAS-301 was somewhat of a surprise and not a good way to begin the year." They added that "in speaking with investors late last year, we got the sense that the trial was likely to succeed," so the failure "highlights our concerns with a weaker pipeline compared to larger-cap biotech peers.

(Also see "*Unhappy New Year For Incyte With Itacitinib Flop*" - Scrip, 3 Jan, 2020.)

Roche's Etrolizumab Flounders In Ulcerative Colitis

In August, the commercial prospects withered for *Roche Holding AG*'s investigational therapy etrolizumab on the failure of its pivotal Phase III trials as a treatment for ulcerative colitis, one of its two possible inflammatory bowel syndrome indications.

Etrolizumab represented Roche's first foray into Crohn's disease and ulcerative colitis, a market that is increasingly competitive, with the advent of products with novel mechanisms and also biosimilar versions of older drugs. Even so, Roche had hoped it could surpass the standard of care and analysts had pegged potential sales of the product in the region of $3bn, and the Phase III read-out was seen as the firm's biggest binary catalyst of the year.

But on 10 August, the Swiss group surprised analysts and investors by saying etrolizumab had failed to meet primary endpoints as maintenance therapy in people with moderately to severely active ulcerative colitis. The data from the program testing it as an induction therapy were also mixed.

The news was a real pipeline setback for Roche, which wants to move beyond its reliance on oncology: cancer drugs represent 45% of the group's revenues.

Etrolizumab is a humanized anti-beta7 integrin subunit monoclonal antibody and the first investigational dual anti-integrin studied in inflammatory bowel diseases (IBD). The product is still in Phase III development for Crohn's disease, with an expected filing in 2022.

(Also see "*Roche's Etrolizumab Failure 'Removes Big Pipeline Opportunity'*" - Scrip, 10 Aug, 2020.)

(Also see "*Roche Has Blockbusters In Its Pipeline – But Demurs On Predicting Hits*" - Scrip, 5 Feb, 2020.)

Novartis Hits Spartalizumab Phase III Setback In Melanoma

That same month, *Novartis AG*'s attempts to enter the PD-1 market by combining its investigational immunotherapy spartalizumab with its Tafinlar and Mekinist BRAF/MEK combination came unstuck, leaving the field to Roche.

Top-line data from the COMBI-i study showed the triple combination missed its primary endpoint of investigator-assessed progression-free survival in patients with previously untreated unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600 mutation-positive cutaneous melanoma, compared with the Tafinlar (dabrafenib) and Mekinist (trametinib) MAPK inhibitor duo alone.

The study was the most advanced for the investigational PD-1 inhibitor – Novartis was late to this area having initially concentrated its IO efforts on its CAR-T therapy Kymriah (tisagenlecleucel), but as with other firms, it planned to develop an in-house anti-PD-1 product for use in combinations, such as with Tafinlar/Mekinist.

The "disappointing and unexpected" failure came shortly after Roche's rival product Tecentriq (atezolizumab) received US Food and Drug Administration approval for use in this setting, under a priority review.

Novartis had hoped to be able to file spartalizumab by the end of the year but said it would continue to test it in a range of tumor types.

The melanoma field has, in any case, become more competitive in recent years. In addition to the MAPK-targeted inhibitors, treatment options also include *Bristol Myers Squibb Company*'s Opdivo (nivolumab), *Merck & Co., Inc.*'s Keytruda (pembrolizumab), and also the Opdivo/Yervoy (ipilimumab) combination, all used in the BRAF V600-positive patient population.

(Also see "*Novartis Hits Spartalizumab Phase III Setback In Melanoma*" - Scrip, 24 Aug, 2020.)

Amgen/Cytokinetics Phase III Heart Failure Data: 'Below Expectations'

Top-line results from the massive Phase III clinical trial of *Amgen, Inc.*'s and *Cytokinetics, Inc.*'s omecamtiv mecarbil in the treatment of heart failure with reduced ejection fraction (HFrEF) disappointed to the extent that Amgen decided to give back its rights to the product.

Released in October, they showed GALACTIC-HF succeeded on the primary endpoint but a crucial secondary endpoint was missed, raising doubts over the selective cardiac myosin activator's future prospects.

The following month, Amgen determined that the results were not compelling enough to move forward with regulatory filings and commercialization of the cardiac myosin activator.

Omecamtiv met the 8,256-patient study's primary composite endpoint of reduction in heart failure events (hospitalizations and other urgent treatments) and cardiovascular deaths with statistical significance versus placebo (HR: 0.92; 95% CI: 0.86, 0.99, p=0.0252). However, it did not show statistical significance on the secondary endpoint of reduction in CV death alone, which is an important data point in the eyes of treating physicians.

Analysts largely deemed GALACTIC-HF a failure based on the secondary endpoint miss and because the 8% relative reduction in hospitalizations and deaths combined was below expectations of about a 15% reduction versus placebo, which would have been viewed as clinically meaningful.

In fact, omecamtiv missed all of the secondary endpoints in GALACTIC-HF and when more detailed results were reported at the American Heart Association annual meeting on 13 November the data showed that there were more deaths from cardiovascular causes in the omecamtiv arm of the study than in the placebo group: 808 deaths (19.6%) versus 798 CV deaths (19.4%), respectively (HR=1.01; p=0.86).

Cytokinetics, however, still believes that it can carve out a commercial niche for omecamtiv in HFrEF patients with lower left ventricular ejection fraction (LVEF) and is evaluating the path forward for the drug.

(Also see "*Amgen/Cytokinetics Phase III Heart Failure Data Are Below Expectations*" - Scrip, 8 Oct, 2020.)

(Also see "*Amgen Hands Omecamtiv Back To Cytokinetics*" - Scrip, 23 Nov, 2020.)

Rethink For Ovid After Angelman Syndrome Drug Disappoints In NEPTUNE

Ovid Therapeutics, Inc. had to hit the pause button on development of its lead asset OV101 (gaboxadol) for Angelman syndrome following the failure of the Phase III NEPTUNE trial, and turn its attention instead to OV935 (soticlestat) for Dravet syndrome and Lennox-Gastaut syndrome.

In December, NEPTUNE missed its primary endpoint of change in overall score on the Clinical Global Impression-Improvement-Angelman syndrome (CGI-I-AS) scale, a novel endpoint which was used for the first time in this study. Among patients who received gaboxadol, there was a 0.7-point improvement, compared with a 0.8-point improvement with placebo. Analysts cited the large placebo effect and the short, 12-week study duration and young patient study population as possible reasons for the failure.

Despite the disappointing results of its attempt to develop the first drug to treat the rare neuro-genetic disorder, Ovid said it hoped the new ground broken with the endpoint may prove useful to followers. Among other drugs in development for AS, at least one – GeneTx Biotherapeutics LLC and Ultragenyx Pharmaceutical Inc.'s GTX-102 – also has CGI-I-AS as an exploratory secondary endpoint in its Phase I/II trial.

Ovid will continue to offer OV101 to Angelman syndrome patients in the Phase II open-label ELARA study, data from which are expected in the first quarter of 2021.

The product also remains in Phase II development for Fragile X syndrome. It was licensed to Italian firm Angelini Labopharm LLC for the EU, UK and Russia, along with options rights for Fragile X syndrome, earlier this year.

(Also see "*Ovid Shifts Focus After Angelman Syndrome Drug Disappoints In Phase III*" - Scrip, 2 Dec, 2020.)

(Also see "*Ovid De-Risks Its Phase III Angelman Program With EU Angelini Partnership*" - Scrip, 13 Jul, 2020.)

HITS

In happier news, there were some standout clinical trial successes in 2020, some of which have already translated to regulatory progress, or at least set the scene for some interesting marketing battles to come. Here are five of the more noteworthy hits.

AZ's Tagrisso Sails Into Early-Stage EGFRm NSCLC

In March, *AstraZeneca PLC*'s 682-patient ADAURA trial of its best-selling product Tagrisso (osimertinib) in the treatment of early-stage non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations was stopped two years ahead of schedule following evidence of "overwhelming efficacy" for the primary endpoint of disease-free survival (DFS).

The data presented at American Society of Clinical Oncology (ASCO) virtual meeting at the end

of May showed that in patients with Stage II and IIIA disease, adjuvant therapy with 80mg Tagrisso once daily reduced the risk of disease recurrence or death by 83% at two years. At the time of data cut-off, overall survival (OS) data favored Tagrisso, but were nowhere near mature (about 5%). The trial is continuing to assess OS as a secondary endpoint.

Just nine months after ADAURA was stopped, the FDA approved the drug – a third-generation EGFR tyrosine kinase inhibitor –for this additional indication on the back of these data, opening a new commercial opportunity for use after surgery where chemotherapy is the current standard of care.

Tagrisso already enjoys blockbuster sales from its two metastatic EFGRm NSCLC treatment settings, generating $3.17bn in the first nine months of 2020. The commercial opportunity in early-stage disease is unlikely to be as lucrative as in metastatic disease, but with ADAURA's 83% relative reduction in DFS, and with the prospect of a slowed disease course or potentially even cures, it is still expected to be substantial. Key to its success here, however, will be increased use of genetic screening for the EFGR mutation in early-stage patients – something which the company hopes will be incentivized by the availability of an approved therapy.

Analysts at Jefferies have predicted adjuvant use to contribute around $3bn to their $9.1bn worldwide peak Tagrisso sales forecast before patent expiries begin, potentially in 2032.

(Also see "*AstraZeneca On Tagrisso's Milestone Advance Into Adjuvant Lung Cancer*" - Scrip, 22 Dec, 2020.)

(Also see "*ASCO 2020: AZ's Tagrisso Sails Into Early-Stage NSCLC On 'Momentous' ADAURA Trial Data*" - Scrip, 29 May, 2020.)

Roche's First Anti-TIGIT Data Support Dual Checkpoint Inhibition Strategy

Moving to novel immuno-oncology targets, the first results for Roche's anti-TIGIT antibody tiragolumab from the Phase II CITYSCAPE study, looking at it in combination with the company's PD-L1 inhibitor Tecentriq (atezolizumab) in first-line metastatic non-small cell lung cancer (NSCLC), showed improved response rates versus Tecentriq alone. There was also a notable improvement in high PD-L1-expressing tumors and no significant additional toxicity for the combination in the data also presented at ASCO.

TIGIT (T-cell immunoglobulin and ITIM domain protein), a receptor found on immune cells, acts as an immune checkpoint. It was discovered by scientists at Roche subsidiary *Genentech, Inc.* who developed tiragolumab to bind with TIGIT, blocking its interaction with the poliovirus receptor, a protein that can suppress the body's immune response. It is hoped that blocking TIGIT and PD-

L1 together may reactivate T-cells and enhance natural killer (NK) cells' antitumor activity.

In CITYSCAPE, the combo showed an overall response rate (ORR) of 37% versus 21% for Tecentriq monotherapy after 10.9 months of follow up. The ORR in patients with PD-L1 expression of 50% or more was 66% for tiragolumab plus Tecentriq versus 24% for Tecentriq alone.

The data supported Roche's decision to move the tiragolumab/Tecentriq combination, which got breakthrough therapy designation from the FDA on 5 January, into two ongoing Phase III trials SKYSCRAPER trials in NSCLC and small cell lung cancer (SCLC).

The dual checkpoint inhibitor strategy could give Roche's Tecentriq a critical boost in PD-1/L1 market share before competing combinations reach the market, since analysts estimate that other anti-TIGIT antibodies are at least a year behind.

However, Merck & Co. Inc.'s TIGIT inhibitor vibostolimab, could prove a threat. Merck is testing it in combination with other checkpoint inhibitors – notably its best-selling Keytruda (pembrolizumab) and a CTLA-4 inhibitor – in NSCLC and melanoma and revealed promising data at ASCO. At least six other firms have anti-TIGIT agents in clinical development.

(Also see "*ASCO 2020: Roche Highlights TIGIT As Tecentriq Bags Another Approval*" - Scrip, 1 Jun, 2020.)

(Also see "*Roche's First Anti-TIGIT Data Support Dual Checkpoint Inhibition Strategy*" - Scrip, 14 May, 2020.)

(Also see "*Merck Is Counting On Keytruda To Establish Its Anti-TIGIT Drug*" - Scrip, 3 Jun, 2020.)

DAPA-CKD Data Put AstraZeneca's Farxiga Out Front

Not content with the success of the landmark DAPA-HF trial in 2019 that opened up a new heart failure market to AstraZeneca's SGLT2 inhibitor, Farxiga (dapagliflozin), the company's DAPA-CKD study managed to repeat the trick in adult patients with chronic kidney disease.

DAPA-CKD was stopped early in March because of "overwhelming efficacy" and results presented at the virtual European Society of Cardiology meeting in August revealed that 10mg/day of dapagliflozin on top of standard of care (ACE inhibitors or ARBs) reduced the risk of a primary endpoint event (a composite of worsening of renal function or risk of cardiovascular or renal death) by 39% compared with placebo. It also reduced the relative risk of all-cause death – a key secondary endpoint – by 31%.

Overall, the data made Farxiga the first medicine to significantly prolong survival in a renal outcomes trial in patients with chronic kidney disease with and without type 2 diabetes.

If successful at the regulators, dapagliflozin will have an edge over its rival SGLT2 inhibitors, *Boehringer Ingelheim GmbH*/*Eli Lilly and Company*'s Jardiance (empagliflozin) and *Johnson & Johnson*'s Invokana (canagliflozin), in this setting, which is likely to prove a sizeable new market. Breakthrough therapy designation and a priority review have been granted by the US FDA and a decision in the supplemental filing is due in the second quarter of 2021.

Farxiga is a key growth driver in AstraZeneca's cardiovascular/renal medicine (CVRM) business and is its top-selling CVRM drug. Estimates put the number of diagnosed patients with chronic kidney disease at more than 4 million in the US alone, with around half also having diabetes, and the additional opportunity could reach $5bn worldwide.

(Also see "*DAPA-CKD Data Put AstraZeneca's Farxiga Out Front*" - Scrip, 31 Aug, 2020.)

(Also see "AZ's Farxiga CKD Trial Hits All Primary, Secondary Targets" - Scrip, 28 Jul, 2020.)

Trodelvy ASCENT Data Could Vindicate Gilead's $21bn Buyout

The Phase III ASCENT study of *Immunomedics, Inc.*'s Trodelvy (sacituzumab govitecan) showed that the antibody-drug conjugate (ADC) doubled OS in heavily pre-treated patients compared with standard treatment in third-line metastatic triple negative breast cancer (mTNBC), achieving 12.1 months survival versus 6.7 months for chemotherapy patients.

The trial was presented at the European Society for Medical Oncology (ESMO) congress in September and confirmed its blockbuster potential in TNBC, with several other earlier-stage studies presented at the meeting consolidating hopes that the Trop2-targeting ADCcould work across a broad range of tumor types.

The data went some way to vindicating *Gilead Sciences, Inc.*'s decision to spend $21bn on buying out Immunomedics in a deal announced the same month, when it described the drug a "pipeline in a product".

Trodelvy received an accelerated approval as a third-line treatment for adult patients with metastatic TNBC in April 2020. The new data will set it up for a full FDA approval, and help it accelerate uptake in the marketplace. The company is also planning to submit a marketing authorization application to the European Medicines Agency in the first half of 2021.

Based on the Phase III data, analysts agreed that Trodelvy has the potential to be used in earlier

TNBC treatment. Studies are already underway in earlier lines of therapy, including the neoadjuvant and adjuvant settings, and in combination with other targeted agents, setting it up to challenge existing therapies such as Roche's PD-L1 immunotherapy Tecentriq . However, Trodelvy will face stiff competition as it expands into other tumor types.

(Also see "*'A New TNBC Standard Of Care' – Trodelvy Could Vindicate Gilead's $21bn Buyout*" - Scrip, 21 Sep, 2020.)

(Also see "*Gilead Buys Pipeline-In-A-Product With $21bn Immunomedics Deal*" - Scrip, 13 Sep, 2020.)

BCMA CAR-T Race Heats Up Between Bristol And Janssen

Another interesting contest involving a novel IO target is shaping up with Janssen (Johnson & Johnson) and Bristol Myers Squibb at the forefront of the race to produce a B-cell maturation antigen (BCMA)-targeting CAR-T therapy. Both reported promising data this year, although the BMS offering seems to have the safety and time-to-market edge.

GlaxoSmithKline plc's ADC Blenrep (belantamab mafodotin) was the first anti-BCMA therapy approved for relapsed or refractory multiple myeloma, but next in line are these two CAR-T therapies, which have shown ORRs more than two to three times the ORR observed for Blenrep in similar heavily pre-treated patient populations. Following them are a number of bi-specific antibody products targeting BCMA heading into Phase II.

In December, longer-term results from the CARTITUDE-1 study reported at the American Society of Hematology meeting for Janssen and *Legend Biotech Corp.*'s ciltacabtagene autoleucel (cilta-cel) showed that multiple myeloma patients treated with the BCMA-targeting CAR-T therapy maintained their responses over time.

The overall response and complete response rates were higher than those observed with idecabtagene vicleucel (ide-cel) from BMS and *bluebird bio*, however, longer-term data for ide-cel showed lower incidences of cytokine release syndrome (CRS) and severe neurotoxicity.

The BMS/bluebird asset also has the benefit of already being under review at the FDA, with a 27 March action date.

As with ide-cel, the agency previously granted a breakthrough therapy designation for cilta-cel in relapsed or refractory multiple myeloma, so with an expedited review it could also be approved in the US in 2021.

(Also see "*ASH 2020: J&J/Legend's Cilta-Cel Shines, But BMS/Bluebird's Ide-Cel Is In First Place*" - Scrip, 5 Dec, 2020.)

(Also see "*ASH 2020: Novel CAR-T Approaches Chase BCMA-Targeting Frontrunners*" - Scrip, 8 Dec, 2020.)

(Also see "*ASH 2020: Bispecifics Battle For Share Of BCMA Market In Myeloma*" - Scrip, 8 Dec, 2020.)