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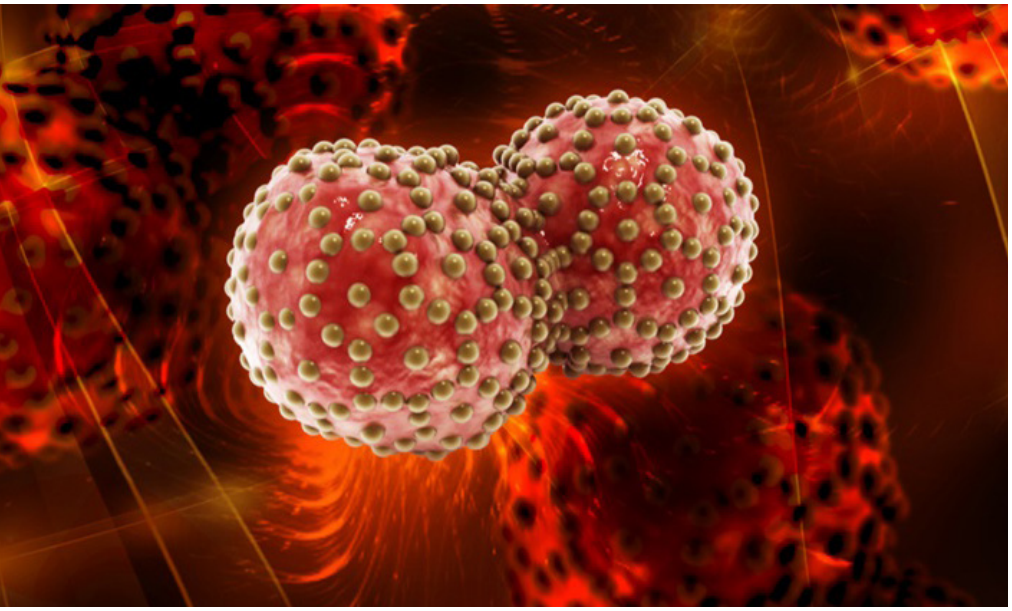

ASCO 2020: AZ's Tagrisso Sails Into Early-Stage NSCLC On 'Momentous' ADAURA Trial Data

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AstraZeneca PLC's top-selling drug Tagrisso (osimertinib) cut the risk of disease recurrence or death by 83% in patients with early stage EGFR mutant non–small cell lung cancer at two years, the first data from the Phase III ADAURA study show.

The initial trial findings, reported at this year's virtual American Society of Clinical Oncology meeting, offer AstraZeneca a new swathe of patients in the EGFR mutated NSCLC market, where the product already enjoys blockbuster sales in two metastatic treatment settings. The challenge for the company now is to encourage increased screening so more early-stage patients can be promptly started on a therapy which, the ADAURA data suggest, could change the course of their disease or even provide a cure.

Surgery is the main treatment for early-stage NSCLC but these patients are not served at present with any targeted therapies in the adjuvant setting. Standard of care here is cisplatin-based chemotherapy, which is recommended for resected patients with Stage II-IIIA disease and for some Stage Ib patients, but rates of disease recurrence and death remain high – there is only about a 5% overall survival benefit at five years for early-stage patients.

The ADAURA investigators said Tagrisso is the first targeted agent to show such an effect in the adjuvant setting and provides an effective new treatment strategy for these patients.

Tagrisso – a third-generation EGFR tyrosine kinase inhibitor – is currently standard of care for advanced EGFR-mutated advanced NSCLC. It was first approved in 2015 for use after disease progression on another EGFR tyrosine kinase inhibitor (TKI) and in 2017 its use was expanded to first-line treatment of advanced patients on the basis of the FLAURA study. Sales have been boosted by the latter setting in particular and reached $982m in the first quarter this year up by 56%, even while it awaits reimbursement decisions in China and Europe.

The 682-patient ADAURA trial sought to test Tagrisso in the earlier setting and just last month was stopped two years ahead of schedule on the recommendation of its independent data monitoring committee following evidence of "overwhelming efficacy" for the primary endpoint of disease-free survival (DFS). *(Also see "AstraZeneca's Oncology Strategy Yields Victories" - Scrip, 13 Apr, 2020.)*

The data being presented at ASCO flesh out the extent of that efficacy. 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% (hazard ratio [HR] of 0.17; 95% confidence interval [CI] 0.12, 0.23; p<0.0001) at two years. This was the study's primary endpoint.

For the broader population that also included patients with Stage Ib disease (a key secondary outcome), there was a 79% reduction in the risk of disease recurrence or death (equal to an HR of 0.21; 95% CI 0.16, 0.28; p<0.0001). Stage Ib patients are more likely to have better

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from the editor

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Last weekend the American Society for Clinical Oncology held its first entirely digital event, abandoning its usual venue, Chicago's McCormick Place, which has been doubling as a field hospital for COVID-19 patients.

The virtual event felt more of a sedate affair than the real thing – you get the data (eventually, despite early technical problems) but you don't get the theatrical buzz of the live presentation in front of a packed audience bursting with questions. We missed the mad dash trying to be in several places at once, collaring experts for a grilling and grabbing a coffee in the press room while figuring out what the hottest sessions are going to be.

Nevertheless, the ultimately successful delivery of sessions and presentations shows that a significant and valuable part of a scientific meeting can be delivered without any physical locus at all, and shared with a far wider community of people around the globe than its on-the-ground counterpart. It will be interesting to see how this year's online-only events influence how future conferences are conducted, once physical distancing rules are relaxed. We have given over the first part of this week's issue to significant updates from the congress; for additional articles visit scripnews.com.

Also inside we bring you the latest updates on the pandemic front, from analysis of pharma's commercial model and how changes thrust upon selling models by necessity may end up persisting for other reasons (p11) to big pharma's latest collaborations on the vaccine/drug R&D front (p12, p16), and more.

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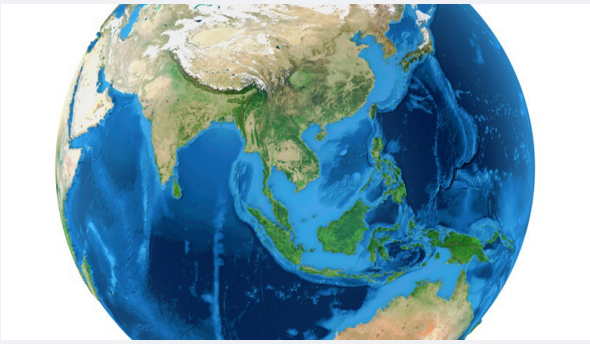

In the third in a popular new series of podcasts, the Asia-based content team for Scrip and the Pink Sheet dissect some of the major events shaping the regional pharma industry over the past few weeks. Unsurprisingly, the coronavirus outbreak remains top of the list.

Join Anju Ghangurde and Vibha Ravi in Mumbai, Brian Yang in Beijing, Jung Won Shin in Seoul and Ian Haydock in Tokyo for a top-line overview of selected key developments.

HOW HAS THE PANDEMIC PLAYED OUT IN COMPANY EARNINGS?

Major Indian and Japanese companies have now reported their annual results for the fiscal year ended 31 March, the end of which overlapped with the full emergence of the virus. Anju and Ian look at the varied business impact so far and what the rest of the year might hold. Are there any common themes emerging?

THE LATEST IN CHINA VACCINE DEVELOPMENTS

Multiple Chinese companies are among the global front-runners in the development of a possible vaccine against SARS-CoV-2. Brian takes us on a tour of local and international R&D developments in the field, and some of the challenges facing developers. (Starts at 11'30")

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To read the rest of this story go to: https://bit.ly/3gJD1pC

inside:

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outcomes and show a lower magnitude of benefit over placebo.

At two years, 89% of Tagrisso patients remained alive and disease-free compared with 53% on placebo. The results were consistent across the subgroups including patients who were treated with surgery followed by chemotherapy and those who received surgery only (see table).

At the time of data cut-off, overall survival (OS) data favored Tagrisso, but were nowhere near mature (about 5%). The trial will continue to assess OS as a secondary endpoint.

The safety profile of the Tagrisso in the study was consistent with previous trials.

So far, the trial data have surpassed its sponsor's and investigators' expectations. AstraZeneca's oncology R&D head José Baselga told *Scrip* that that he did not remember ever seeing such a hazard ratio in a study in a solid tumor.

"When you look at these curves … I've never seen anything like this. The first thing you realize hopefully there are going to be a number of patients where the disease will not come back," he said. "What we are doing is we are doubling down on our philosophy that we need to intervene earlier … I think this dataset proves the principle that when you intervene early you can cure patients."

ADAURA's principle investigator Roy Herbst of Yale Cancer Center said the hazard ratio for the primary outcome was three to four times better than had been anticipated. "Adjuvant osimertinib provides a highly effective, practice-changing treatment for patients with Stage Ib, II, IIIa EGFRm NSCLC after complete tumor resection," he said.

ADAURA Efficacy Data

	TAGRISSO	PLACEBO
DFS Stages II-IIIA (primary endpoint)[i]	(n=233)	(n=237)
HR (95% CI)	0.17 (0.12, 0.23)	
p-value	p<0.0001	-
DFS rates (95% CI)	-	-
One year	97% (94%, 99%)	61% (54%, 67%)
Two years	90% (84%, 93%)	44% (37%, 51%)
Three years	80% (68%, 88%)	28% (19%, 38%)
DFS Stages IB-IIIA (secondary endpoint)[i]	(n=339)	(n=343)
HR (95% CI)	0.21 (0.16, 0.28)	-
p-value	p<0.0001	-
DFS rates (95% CI)	-	-
One year	97% (95%, 99%)	69% (63%, 73%)
Two years	89% (84%, 92%)	53% (47%, 59%)
Three years	79% (69%, 86%)	41% (33%, 49%)

[i] The data cut-off date for DFS was 17 January 2020. Source: AstraZeneca

SALES BOOST

The duration of treatment offered by the earlier settings should support additional blockbuster sales, and AstraZeneca is discussing the data with regulators with plans to file for expanded approval later this year.

How soon any approval could come is a key question. "These results will likely be practice changing, but the OS data is still immature and it remains to be seen if the DFS data alone will be sufficient for regulatory approval," said Datamonitor Healthcare analyst Tara Hansen.

But analysts at Jefferies and Credit Suisse agree that the data are likely strong enough to change clinical practice even in the absence of OS data. "Multiple agents have previously failed to show a signal in adjuvant EGFR mutant lung cancer so the depth and breadth of this response is extremely impressive," said Credit Suisse in a 28 May note. They also said that they saw little cannibalization on the drug's metastatic use.

Jefferies analysts added, "[The] data are compelling and in our view likely sufficient to sway early doctor adoption, ahead of OS results that are normally the gold standard in the adjuvant setting." Given Tagrisso's profound benefit in ADAURA they assume regulators will seek to fast track approvals, "albeit some physicians are likely to start adopting the drug after this weekend's ASCO presentation."

They forecast adjuvant use to contribute around $3bn to their $9.1bn worldwide peak Tagrisso sales forecast before patent expiries begin potentially in 2032.

SCREENING NEEDED

However, there is the matter of finding the patients. Dave Fredrickson, head of AstraZeneca's oncology business unit, said that the company estimated that there are around 60,000 patients with resectable Stage Ib to IIIa EGFR mutation NSCLC in the US, Japan, China and Europe, which amounts to about "a quarter of the size of the stage IV metastatic setting where we have the FLAURA indication."

He told journalists during a pre-ASCO briefing that the hope was that the data from ADAURA would lead to a greater focus and emphasis on early screening "and so I would hope to see that number increase."

However, he admitted, increasing diagnoses at early stages would take a concerted effort. "It is results like these that create the impetus to make sure we are driving these screening efforts but again it is an important and significant undertaking," he said.

Nevertheless, Credit Suisse was optimistic that AstraZeneca would succeed. "This is not standard practice today simply because it would not inform any treatment option. With efficacy of this magnitude, we expect rapid adoption of testing. Physicians are very familiar with the EGFR test from the metastatic setting so we see limited barriers."

NEXT STEPS

AstraZeneca is looking to take Tagrisso even earlier in the treatment paradigm for EGFR mutated NSCLC patients, and has started the NEO-ADAURA study in the neo-adjuvant setting.

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Merck's Keytruda Doubled PFS In Some Colorectal Cancer Patients In ASCO Late-Breaker

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Merck & Co. Inc.'s Phase III KEYNOTE-177 trial studying its PD-1 therapy Keytruda (pembrolizumab) versus chemotherapy showed the cancer immunotherapy should be the new standard of care for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) unresectable or metastatic colorectal cancer, lead investigator Thierry André, Sorbonne Université, told a press briefing ahead of the opening of the American Society of Clinical Oncology (ASCO) virtual meeting.

KEYNOTE-177 – one of seven late-breaker abstracts featured by ASCO – is the first Phase III trial to study Keytruda as a monotherapy versus standard of care (chemotherapy plus bevacizumab or cetixumab) as first-line therapy in MSI-H metastatic colorectal cancer.

Merck already announced in April that the blockbuster drug significantly improved PFS over chemotherapy in the KEYNOTE-177 trial in MSI-H or dMMR unresectable or metastatic colorectal cancer, but presented the details for the first time at ASCO. Keytruda is currently approved for use in MSI-H/dMMR patients regardless of tumor origin, but only after those patients have failed other options, so the positive results of the trial will likely pave the way for earlier use in the colorectal cancer setting.

"Pembrolizumab should be the new standard of care for these patients," André said. "After stopping pembro, some patients were cured of metastatic disease. These data present another step forward for biomarker-driven studies." Impaired DNA mismatch repair and the resulting high microsatellite instability are thought to sensitize a tumor to treatment with immuno-oncology in a cancer type that may not normally be susceptible to IO, spurring research into patients with these markers regardless of tumor type.

"It is practice changing, I agree with that. It sets a new standard for that subpopulation," MD Anderson Cancer Center's Michael Overman, who will be the discussant for the presentation at ASCO, told *Scrip*.

A PLEA FOR MORE BIOMARKER-LED RESEARCH

While Overman commended that KEYNOTE-177 was a biomarker-driven study, he does argue that there should be more tumor-agnostic studies, like the indication Keytruda already has for second-line treatment. In 2017, Keytruda became the first cancer therapy approved by the US Food and Drug Administration for use based on a biomarker regardless of tumor type. At the time, the approval was hailed as a milestone in cancer treatment because it was based on a common biomarker rather than the location in the body where the tumor originated.

More tumor-agnostic studies would mean "it's not just the common cancers that get immuno-oncology earlier – it should be the same for rare cancers," he said.

Still, KEYNOTE-177 "is really the first solid biomarker-driven success [for immuno-oncology] to some degree," Overman added. PD-L1 and tumor mutation burden (TMB) are not unequivocally successful, and "don't really cleanly define [patient selection] in a black and white scenario. MSI-H and dMMR does. We've been able to take a biomarker and move that group from a standard of chemo to a standard of immunotherapy, which itself is a pretty extreme change," the clinician said.

MSI is a change that occurs in the DNA of certain cells (such as tumor cells) in which the number of repeats of microsatellites (short, repeated sequences of DNA) is different from the number of repeats that was in the DNA when it was inherited, as defined by the National Cancer Institute. The cause of microsatellite instability may be a defect in the ability to repair mistakes made when DNA is copied in the cell. The defect is also referred to as dMMR.

Approximately 10%-15% of colorectal cancer patients have tumors that score as either MSI-H or dMMR when testing is performed, according to Merck. Treatment guidelines for CRC already call for testing for MSI or dMMR, which can be done in local labs. KEYNOTE-177 used local lab testing, which Overman commented made it a real-world study of testing.

DRAMATIC IMPROVEMENT IN PFS

The detailed KEYNOTE-177 results showed that treatment with pembrolizumab doubled progression-free survival versus standard of care (16.5 months versus 8.2 months). In the study, 48.3% of patients treated with Keytruda maintained PFS at 24 months versus 18.6% of patients treated with chemotherapy alone.

Keytruda had a higher overall response rate versus chemotherapy, at 43.8% versus 33.1%, and the responses were more durable. The median duration of response was not reached in the Keytruda arm but was 10.6 months in the chemotherapy arm. Overall survival, the dual primary endpoint, is continuing to be evaluated.

However, Overman noted that the progressive disease rates are cautionary. Chemotherapy was better until six months, "so you do have some patients that are non-responsive and progress out of the gate – there's a subset that doesn't respond and we need to identify that." This suggests that in a patient where initial response is important – a very symptomatic patient with a high disease burden who may not be alive in a few months, "maybe do chemo first and then [immunotherapy]."

Keytruda also demonstrated an improved safety profile versus chemotherapy in the KEYNOTE-177 trial, with a lower incidence of grade ≥3 treatment-related adverse events (22% versus 66%).

The safety profile is remarkable, Overman said. "We get better therapy with massively lower toxicity. That's just amazing. The toxicity profile is just dramatically lower," especially compared to the option for second-line treatment of MSI-H or dMMR metastatic CRC, for which Bristol's Opidvo (nivolumab) is approved, alone or in combination with its CTLA-4 inhibitor Yervoy (ipilimumab)

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Additional reporting by Mary Jo Laffler (maryjo.laffler@informa.com)

Allogene Takes Step Closer To Off-The-Shelf CAR-Ts

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Allogene Therapeutics Inc. made a splash at the American Society of Clinical Oncology's virtual annual meeting with early data that support the viability of its off-the-shelf chimeric antigen receptor T-cell (CAR-T) therapeutic in lymphoma, potentially with improved safety and comparable efficacy to autologous CAR-T therapies, albeit across different lymphoma types.

Since the introduction of the first personalized CAR-T therapies, manufactured for individual treatment using the patient's own cells, there has been demand for an off-the-shelf, allogeneic version with easier manufacturing that could work for solid tumors. Allogene formed in 2018 as former executives from CAR-T pioneer Kite Pharma Inc. took over a pipeline of allogeneic CAR-T assets from Pfizer Inc. *(Also see "'We Jumped' At Opportunity To Take On Pfizer's CAR-T Program, Allogene's Chang Says" - Scrip, 4 Apr, 2018.)*

"The promise of allogeneic CAR-T to create a drug-like treatment modality has been delayed for some time, but we now see a decent size proof of concept," Bernstein analyst Ronny Gal said in a 30 May note on the ASCO virtual meeting. Ultimately, he deemed the Allogene data "nothing to pick at, but we need to see the results by tumor type."

Canaccord Genuity analyst John Newman commented in a 29 May note that "we now await additional follow-up data to determine the durability of responses, in order to better evaluate efficacy vs. prior autologous data."

During a same-day investor presentation, Allogene chief medical officer Rafael Amado noted that in CAR-T-naïve patients, the initial responses in the Phase I ALPHA trial were comparable to autologous CAR-T therapies. Objective response rates (ORR) ranged from 70% to 83% across dose groups for ALLO-501, administered after treatment with the company's anti-CD52 agent ALLO-647 for lymphodepletion, versus 64%-80% in autologous Phase I trials in non-Hodgkin lymphoma and 50%-73% in autologous Phase II trials in NHL. Initial safety data from ALPHA also compare favorably to autologous therapies.

That's on top of the other potential benefits – successful manufacturing for all patients, only five days to treatment and easy re-dosing. CEO David Chang started out the call reviewing "why we believe allogeneic cell therapy will lead the revolution," from improved access to speed and reliability to scalable manufacturing and lower ancillary costs.

"ALLO-501 should minimize time waiting for treatment, during which disease can progress, as lymphodepletion began five days after enrollment," Canaccord's Newman said. "Patients often wait 15-54 days to receive autologous CAR-T therapy … during which cancer can progress."

THE ALPHA DATA

The Phase I ALPHA study of ALLO-501 with ALLO-647 enrolled heavily pretreated patients with advanced-stage disease, either follicular lymphoma or diffuse large B-cell lymphoma; the company said efficacy was consistent across FL and DLBCL, but analysts would like to see separate datasets.

Fourteen of the patients (64%) were chemo-refractory. Four patients had prior autologous CAR-T therapy, two with short-lasting partial responses as their best response and two with progressive disease as best response to autologous CAR-T. Nineteen patients were included in the efficacy dataset and all 22 treated patients were part of the safety dataset.

There were no dose-limiting toxicities and importantly no graft-versus-host disease. Allogene has built in TALEN gene edits to control GvHD and graft rejection. ALPHA investigator Sattva Neelapu, MD Anderson Cancer Center, noted that cytokine-release syndrome – an important adverse event for CAR-T – was manageable.

Anti-tumor activity was seen across all dose levels, and AlloCAR-T cell expansion was associated with responses. All told, the ORR was 63% (12/19 patients) with 37% having complete responses (CR). Nine of 12 responders remain in response, Neelapu reported, and one patient was retreated with ALLO-501 (120 x 106) and fludarabine, cyclophosphamide and ALLO-647. That patient later achieved a CR.

Canaccord's Newman pointed out that "two patients converted an initial partial response to a complete response, suggesting continuing activity, as has been seen for autologous products."

LYMPHODEPLETION = DEEPER RESPONSE

Higher-dose ALLO-647 appeared to be associated with deeper responses (50% CR), nearly twice the 27% seen at the lower dose, Neelapu reported.

"Lymphodepletion seems to drive better quality responses," Jeffries analyst Biren Amin said in a 29 May report. He sees Allogene's lymphodepletion strategy as "key to achieve durable responses and differentiate from other allogeneic programs," as other CD19 allogeneic CAR-Ts have not used an anti-CD52 partner for lymphodepletion.

"Stringent [lymphodepletion] conditions eliminated host immune cells more thoroughly, allowing enhanced intratumoral proliferation of CAR-T cells to drive deeper responses. The data suggest that host lymphodepletion is not only an obligatory component of curative T-cell therapy, but also the key factor to optimize on duration," Amin explained.

H.C. Wainwright analyst Debjit Chattopadhya similarly commented on the value of ALLO-647, which he noted is leveraged across Allogene's platform for hematologic malignancies.

Allogene is testing another version of ALLO-501 (501A) that does not have rituximab recognition domains, which "we believe will allow for use in a broader patient population, including those NHL patients with recent rituximab exposure," Chang explained. An "abbreviated" Phase I trial is enrolling and the next-generation 501A, to which Servier holds rights outside the US, will move into Phase II.

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Bavencio's Survival Benefit Confirmed In Front-Line Maintenance Therapy For Advanced Urothelial Cancer

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Merck KGaA/Pfizer Inc.'s checkpoint inhibitor Bavencio (avelumab) is the first immune therapy to show a survival advantage in advanced bladder cancer when given as front-line maintenance therapy, further clinical data reported at ASCO have confirmed, and Bavencio appears to lead potential immune-oncology competitors in this setting.

Further details of avelumab's effects in urothelial carcinoma come from the JAVELIN Bladder 100 study, to be presented during a 31 May plenary session at this year's virtual annual meeting of the American Society of Clinical Oncology (ASCO). Also being presented during ASCO are clinical data on avelumab therapy being associated with durable clinical responses in gestational trophoblastic neoplasia, from the TROPHIMMUN Phase II study.

Top-line results from the JAVELIN Bladder 100 study were announced in January, and a supplemental US BLA was submitted in April for the use of avelumab for the first-line maintenance treatment of urothelial carcinoma patients; the submission is being evaluated under the FDA's Real-Time Oncology Review (RTOR) pilot program, which can lead to speedy approvals.

> "This is the first time that an immune therapy clinical trial has shown a survival benefit for first-line therapy in metastatic bladder cancer." - Thomas Powles, principal investigator

Bavencio is already approved by the US Food and Drug Administration for urothelial cancer, but that was based on an expedited Phase I trial as a second-line therapy in patients with disease progression after front-line chemotherapy, and the product has struggled to compete with other anti-PD1/PD-L1 agents already available for this indication.

In the EU, avelumab is currently approved for metastatic Merkel cell carcinoma, and for use in combination with axitinib for first-line treatment of advanced renal cell carcinoma.

In 2019, avelumab's worldwide sales reached €103m, a long way behind the multi-billion dollar revenues achieved by other checkpoint inhibitors, but the product's momentum is growing, with sales in the first quarter of 2020 reaching €33m, up by 50%.

In the 700-patient Phase III JAVELIN Bladder 100 global study, avelumab was associated with a 31% reduction in the risk of death in patients with locally advanced or metastatic urothelial carcinoma previously treated with a platinum-containing chemotherapy and gemcitabine, whose disease did not progress on that chemotherapy.

Median survival was extended by more than seven months, from 14.3 months in patients treated with best supportive care to 21.4 months in patients given best supportive care plus avelumab.

In patients positive for PD-L1, avelumab plus best supportive care significantly prolonged overall survival, and median overall survival has not yet been reached. Median overall survival was 17.1 months in such patients treated with best supportive care alone. In all patients, and in those with PD-L1-positive tumors, progression-free survival was better with avelumab than with best supportive care.

Adverse events of grade 3 or higher were reported in 47.4% of avelumab-treated and 25.2% of placebo-treated patients, most commonly urinary tract infections, anemia, hematuria, fatigue and back pain.

PRACTICE CHANGING

"This is the first time that an immune therapy clinical trial has shown a survival benefit for first-line therapy in metastatic bladder cancer," said principal investigator Thomas Powles, professor of genitourinary oncology at Queen Mary University of London. This immunotherapy has the potential to be practice-changing for patients, he added. While avelumab has already been shown to be effective in metastatic disease, this study reports the first data demonstrating efficacy of front-line treatment in the period following initial chemotherapy. "The maintenance setting is an attractive time for using a checkpoint inhibitor. Patients have gone through chemotherapy and the disease is under control," Powles said. "But instead of waiting for disease to progress after chemotherapy, which it will quickly do in patients with advanced urothelial cancer, adding avelumab significantly improves survival."

However, avelumab may not be unique with regard to use first-line in advanced bladder cancer, Powles has suggested. "As it currently stands, I see more similarities than differences with the immune checkpoint inhibitors in urothelial cancer," he told an ASCO press briefing. "We now have positive randomized Phase III trials for pembrolizumab (Merck & Co. Inc.'s Keytruda), avelumab and atezolizumab (Roche's Tecentriq) all in slightly different settings, and currently it is much easier to make the argument that all the drugs seem to work in a similar kind of way."

He continued: "The differences we see are probably more likely due to the trial design and the biomarker that is being used rather than differences between the drugs … [even so] I don't think one should universally pile in and say all the drugs should be used equally in this setting until they have been shown to be active."

Other commentators noted that the ADAPT data presented at ASCO were still immature. "The secondary endpoints of disease control rate and objective response rate have not been discussed, and OS findings from patients who crossover from the control arm to the avelumab arm are yet to be seen, so we await further announcements before a full appraisal can be made," pointed out Datamonitor Healthcare analyst Tom Tyler.

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ASCO 2020: Can Xtandi PROSPER In Prostate OS Data Battle?

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Final results from the overall survival (OS) analysis of the Phase III PROSPER trial with Pfizer Inc. and Astellas Pharma Inc.'s Xtandi (enzalutamide) show the drug plus androgen deprivation therapy (ADT) significantly extended this secondary endpoint in non-metastatic castration-resistant prostate cancer (nmCRPC).

But market rival Janssen Pharmaceutical Cos.'s Erleada (apalutamide) showed an even longer extension in the same secondary endpoint in its trial, as the important data are reported to the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting.

In PROSPER, enzalutamide reduced the risk of death by 27% (hazard ratio=0.73; 95% confidence interval: 0.61-0.89; p=0.001) compared to placebo plus ADT. The median OS was 67.0 months (95% CI: 64.0 to not reached) for men who received Xtandi plus ADT, compared to 56.3 months (95% CI: 54.4 to 63.0) for placebo plus ADT.

In findings published in 2018, PROSPER met its primary endpoint of metastasis-free survival (MFS), showing a significant reduction in the risk of developing metastasis or death with Xtandi plus ADT versus ADT alone in the indication (HR=0.29; 95% CI: 0.24-0.35; p<0.001).

The important OS data, presented to ASCO's virtual scientific program and simultaneously published online in the *New England Journal of Medicine*, provide further support for the anti-androgen therapy's position in the first-line setting. But how they will stack up against the new Erleada data among physicians remains to be seen.

Xtandi was a significant driver behind Pfizer's $14bn acquisition of Medivation Inc. in 2016 and Pfizer has said that expansion into the non-metastatic population would double the commercial opportunity for the drug. In the US alone, there are 30,000-35,000 patients with nmCRPC.

Xtandi was approved in the US in July 2018 for both metastatic and non-metastatic CRPC and then in the EU for nmCRPC that October. But Erleada beat it to the US market in this indication, for which it received FDA approval in February 2018. The drug has just been approved in Japan for prostate cancer patients with distant metastasis, adding to its current indications of metastatic hormone-sensitive prostate cancer and castration-resistant prostate cancer. The new indication nod was based on results from the Phase III ARCHES and ENZAMET trials.

SPARRING WITH SPARTAN

Ahead of ASCO on 14 May, Janssen announced OS results from a final analysis of the pivotal Phase III SPARTAN study for its anti-androgen molecule apalutamide in combination with androgen deprivation therapy (ADT), which again showed significantly improved OS compared to ADT alone in nmCRPC patients at high risk of developing metastases.

SPARTAN showed that apalutamide plus ADT prolonged median OS by 14 months and decreased the risk of death by 22%. Median OS was significantly longer, at 73.9 months for apalutamide/ADT versus 59.9 months for placebo/ADT (HR=0.78; p=0.0161 (to reach statistical significance, a p-value of p<0.046 needed to be observed)).

Both the absolute OS value and extension over placebo were longer than for enzalutamide, by 6.9 months and 3.3 months respectively.

After the study met its primary endpoint of MFS (the same as in the PROSPER trial), SPARTAN was unblinded and patients on placebo were allowed to cross over to apalutamide. The OS results were achieved despite a crossover of 76 randomized placebo patients (19%) to apalutamide, Janssen noted.

After adjusting for the cross-over of patients in the placebo arm, the treatment effect of apalutamide plus ADT still exceeded median OS compared to placebo plus ADT, with a difference of 21 months between the two arms (73.9 months vs 52.8 months, respectively, HR=0.69, p=0.0002).

Additionally, treatment with apalutamide in combination with ADT significantly delayed patients' time to cytotoxic chemotherapy compared to placebo in combination with ADT (HR=0.63; p=0.0002).

'SIGNIFICANT IMPROVEMENT' FOR NUBEQA

Meanwhile, Bayer AG/Orion Corp., as other newer contenders in the crowded prostate cancer market, announced on 13 May that their oral androgen receptor inhibitor Nubeqa (darolutamide) plus ADT demonstrated a "significant improvement" in OS compared to placebo plus ADT, with a 31% reduction in risk of death (HR=0.69; 95% CI 0.53-0.88; p=0.003).

The top-line results came in a pre-specified final OS analysis from the Phase III ARAMIS trial, which again had MFS as the primary endpoint. Further details of the actual benefits will be presented at ASCO following other results from the study released last year. Nubeqa was approved in the US last July for men with nmCRPC at high risk of developing metastatic disease and is also approved in the EU (this March) and several other major markets.

Published online 1 June 2020

Other ASCO Coverage

Kura May Have Found A Place For Tipifarnib In Head-And-Neck Cancer: https://bit.ly/2Mjvaks

DESTINY Calls For Daiichi Sankyo/AZ's Enhertu In Other Indications: https://bit.ly/36PFeuT

ASCO 2020: Roche Highlights TIGIT As Tecentriq Bags Another Approval: https://bit.ly/3eJkGa6

'Business Unusual': COVID-19 Brought Commercial Changes To Pharma And It May Stick

JESSICA MERRILL Jessica.merrill@informa.com

The pharmaceutical commercial model could be in for changes that persist well beyond the initial months of the COVID-19 pandemic. The consulting firm ZS Associates is advising industry to expect long-term modifications to the pharma selling model, after conducting research with more than 100 patients and 100 physicians, and hosting a virtual roundtable discussion with biopharma executives.

The COVID-19 outbreak in the first quarter of 2020 led patients to skip going to see the doctor and kept sales reps out of doctors' offices too, which is expected to have some impact on pharmaceutical sales in the second quarter, even though the drug industry was generally resilient financially in the first quarter. Changes that have come about because of the pandemic around telemedicine and virtual doctor's visits – or patients just plain skipping visits – could persist longer-term, according to ZS.

"This will probably continue in some measure for at least a year/year-and-a-half," ZS Managing Principal Pratap Khedkar said in an interview, referencing the social distancing in physician practices and patients sitting out non-priority doctor visits.

"At the other end of this eventually with a vaccine, we then enter the new normal, which is things will go back partially but not completely because what was changing because of fear will remain changed because of habit." As Khedkar calls it, "business unusual."

Digital health services provider Epion Health – which provides digital solutions to health care providers to collect information from patients and also offers a telemedicine platform – said it expects the short-term impact of COVID-19 will result in a long-term bounce for telehealth. In 2019, 1% of physician visits were telehealth but that jumped to 70%-80% in April, chief operating office Scott Freedman said in an interview.

"We don't have a crystal ball, but I think it is going to be in the double-digits," he said. "Whatever it is, I think it is going to be substantial enough where our clients are having to balance appointments and think about the balancing of appointments between the two, whereas previously most didn't."

ADJUSTING TO A NEW NORMAL

Drug companies should be laying the foundation now to meet the needs of patients and physicians when the new normal materializes, ZS Associate's Khedkar advised.

The impact of COVID-19 will be felt more heavily in some therapeutic areas than others. In a poll conducted by ZS Associates in April of 102 physicians across therapeutic specialties, endocrinologists and rheumatologists said they expected to have the highest percentage drop in diagnosis and treatment initiation of new patients versus pulmonologists, neurologists, cardiologists, infectious disease specialists, oncologists and primary care physicians. Rheumatologists, in particular, said they expected a notable decline in patient diagnosis (49%) and treatment initiation for new patients (45%). Endocrinologists said they expect a decline of 31% and 25%, respectively.

Some of that is driven by drug administration and also concerns about how vulnerable a patient population is to COVID-19. Well known oral medications are expected to be less impacted than medications that are infused in infusion centers or physician offices, for example. Oncologists also expect some impact, including a 24% decline in new patient diagnosis and a 14% decline in new treatment initiation, though there is likely to be urgency to return to treatment sooner.

Geographic differences also need to be taken into account. A follow up poll of 400 patients and physicians conducted by ZS found that while 74% of doctor's visits are remote visits in areas heavily impacted by COVID-19 like New York, New Jersey and Pennsylvania, in other parts of the US only about 59% of physician visits are remote.

"The question is when social distancing is relaxed a little bit and we do open up … will the patient come back? I think our research is indicating that yeah, many patients will come back, but maybe a quarter of the patients roughly will not come back for a long time, especially if their disease is not something that is life threatening," Khedkar said.

On the commercial side, pharmaceutical executives need to be thinking about ways to address the barriers – structural and psychological barriers. For example, Khedkar said, industry is starting to think about more creative ways it can help patients maintain therapy or even get started on a new therapy. For example, he said, there may even be opportunities to partner with payers or integrated delivery networks (IDNs) in a way that neither side would have been open to before. Perhaps sales reps could be repositioned in a way to provide additional patient support as opposed to just staying at home.

Providers too may be feeling resource constrained because they are losing money as patients stay home. Even while a lot of the industry backed away from physicians' offices amid the COVID-pandemic – in some cases out of courtesy to give physicians time to focus on how they would handle issues around the pandemic – some physicians actually ended up having more time because their patient load diminished.

"Continuing to engage the physicians, understanding what their specific problems are and figuring out if pharma can come up with creative ways to help them, I think, is very much the order of the day," Khedkar said.

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Latecomer Merck Enters Coronavirus Vaccine Field With Themis Acquisition

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Merck & Co. Inc. has been conspicuous by its absence to date from the race to develop COVID-19 vaccines and therapies – but has now unveiled a three-part strategy to tackle the pandemic.

This will entail the acquisition of privately held vaccines firm Themis, which already has a novel coronavirus candidate in pre-clinical testing with France's Institut Pasteur.

That won't put Merck into contention to be among the potential first developers of a vaccine which could reach patients in 2020 - such as Moderna Inc. and the University of Oxford and AstraZeneca PLC - but it clearly believes that a somewhat slower approach will pay off in the long run.

Secondly it has also launched a new alliance with non-profit research organisation IAVI to develop a vaccine using the same recombinant vesicular stomatitis virus (rVSV) technology Merck used to develop its Ebola vaccine. *(Also see "Merck's Ervebo Becomes World's First Approved Ebola Vaccine " - Scrip, 12 Nov, 2019.)*

Merck has also signed an agreement with the US Biomedical Advanced Research and Development Authority (BARDA) to provide initial funding support for its work with IAVI.

Finally, Merck has also unveiled an alliance with US-based Ridgeback Bio to develop a novel antiviral candidate – highlighting the need for these products, as limitations of Gilead's remdesivir have come into sharper focus in recent days.

Ridgeback's EIDD-2801 is a ribonucleoside analog currently in Phase I studies, and could be given as an oral treatment. It has been shown to inhibit the replication of multiple RNA viruses including SARS-CoV-2.

MERCK'S VACCINE EXPERTISE

The US company is one of the world's biggest pharma companies and in the 'big five' biggest vaccines manufacturers alongside GSK, Sanofi, Pfizer and J&J.

Those companies are all well advanced in their efforts to develop a SARS-CoV-2 vaccine, but Merck had deliberately held back on committing itself to the field since the novel virus emerged in January.

The company's chief executive Kenneth Frazier and president of research Roger Perlmutter indicated earlier this month that they were wary of rushing into research commitments before enough was known about SARS-CoV-2, and would take a considered approach to selecting R&D projects.

Merck is particularly well versed in the difficulties of developing vaccines against novel viruses – in November 2019 it gained approval for Ervebo, the world's first vaccine against Ebola. It was developed with the help of Canada's National Microbiology Laboratory and funding from BARDA and took was the culmination of two decades of research before it gained approval.

Announcing the COVID-19 strategy, Frazier's remarks hinted at a defense of this slower approach, saying the company was "proud to mark the culmination of our swift, conscientious and concerted effort" to tackle the virus, and said it had been "fully committed to an effective response" since COVID-19 was first identified.

"With our singular legacy and expertise in vaccines and anti-infective medicines, we know Merck has a responsibility to engage in the scientific community's efforts to find new medicines and vaccines to bring this pandemic to an end," said Frazier.

THEMIS ACQUISITION GOES BEYOND COVID-19

The acquisition of Vienna, Austria-headquartered Themis Bioscience GmbH gives Merck an immediate stake in the race to develop a COVID-19 vaccine, but also adds a new team of researchers specializing in the broader field of immunomodulation therapies for infectious diseases and cancer.

Its modified measles virus vaccine can be engineered to express a wide range of antigens. It has already been incorporated into development programs against infectious diseases including SARS, Chikungunya, MERS and Lassa fever.

The companies are already collaborating to develop vaccine candidates using this platform, and are expected to accelerate the development of Themis's COVID-19 vaccine candidate.

Themis recently entered into a collaboration with Institut Pasteur, the Center for Vaccine Research at the University of Pittsburgh and the Coalition for Epidemic Preparedness Innovations (CEPI) to develop its COVID-19 vaccine candidate.

The vaccine candidate is in preclinical development, and clinical studies are planned to start later in 2020.

Merck is likely to face the same range of demanding issues as its big pharma peers in the field in trying to develop a vaccine against SARS-CoV-2.

These include the challenge of running Phase III vaccine trials against a rapidly diminishing number of active cases in regions such as the US and Europe. This will make it difficult to generate data proving the vaccine can protect against infection – a problem also seen in the unpredictable Ebola virus – and could hold back efforts to gain final approval for COVID-19 vaccines.

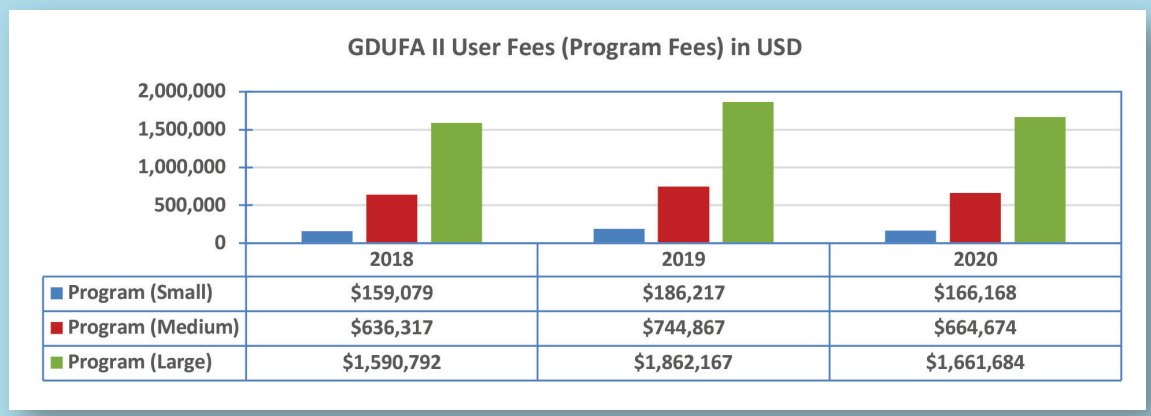
Published online 26 May 2020

Park Unused ANDAs Here

For GDUFA II Program Fee Relief

GDUFA II User Fees: They Saved Paradise and Put Up a Parking Lot

The Generic Drug User Fee Amendments ("GDUFA") payment due date has just passed — the first business day on or after October 1st of each year — and companies are trying to plan ahead now in 2020 to see if there's a way to reduce costs and save money. Fees can be dramatic and impactful just to keep the assets you own already and worked so hard to develop or acquire.



	2018	2019	2020
Program (Small)	$159,079	$186,217	$166,168
Program (Medium)	$636,317	$744,867	$664,674
Program (Large)	$1,590,792	$1,862,167	$1,661,684

This is true especially for a company in the small and medium size operation tiers—and perhaps one or two in the large size operation tier — seeking a way to potentially save significant program fees. A few years ago, a system dubbed "ANDA Arbitrage" was introduced by a company called **ANDA Repository, LLC** in an effort to help companies potentially decrease annual user fee liability under GDUFA II.

Imagine a parking lot. The owner of a car that is not being used on a daily basis needs a parking space for that car. In exchange for that parking space (and an annual fee) the car's owner transfers title of the automobile to the parking lot owner. The former owner of the car can, with appropriate notice, take back ownership when he decides he wants to use the automobile again. Provided the parking lot owner has enough cars in the lot, this can be a beneficial venture for all of the parties involved.

In the imagery above, the automobile owner is an ANDA sponsor (typically with a discontinued, but not withdrawn approval, ANDA), and the parking lot owner and attendant is **ANDA Repository, LLC**. As a "large size" operation, ANDA Repository, LLC pays a flat GDUFA II ANDA Holder Program Fee regardless of how many ANDAs are owned. In exchange for its services, ANDA Repository, LLC charges an ANDA sponsor an annual fee, which is significantly less than the ANDA Holder Program Fee the ANDA sponsor would otherwise pay as a small or medium size operation.

If you're interested in the program, please reach out to ANDA Repository, LLC soon. The mechanism to communicate to the FDA a transfer in ANDA ownership well prior to October 2020 is relatively painless. Also please check with us before WITHDRAWING your ANDAs. There were 388 ANDA Withdrawals last fiscal year, which is like burning your own assets. Unless mandated to do so, **ANDA Repository** is a far better option, and we may be interested in purchasing them from you outright. Contact us NOW!!!

Phone: +1-570-261-1901 | Email: info@andarepository.com

US Phlow Model And Drug Nationalism: Do Indian Firms Need To Be Watchful?

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US federal backing for local start-up Phlow Corp. is generally seen as part of COVID-19-related "medicines nationalism" playing out as the US seeks to lower dependency on foreign nations to support its drug supply chain.

The collaborative effort, touted as a "defining moment and inflection point" for safeguarding the country from future public health threats, intends to bolster medicines security and provide a solution to combat chronic generic drug shortages in the market.

The initial federal funding for Phlow of $354m is being routed through the Biomedical Advanced Research and Development Authority (BARDA) and the new company is partnering with AMPAC Fine Chemicals, Civica Rx and Virginia Commonwealth University's Medicines For All Institute.

While a single start-up is unlikely to markedly impact supply dynamics instantly, the Phlow-model probably isn't something that pharma firms in India - some of which derive a significant share of their revenues from the US - will want to ignore. Particularly if Phlow-like initiatives catch on as countries re-prioritize healthcare amid the pandemic and see merit in end-to-end drug manufacturing on home turf.

For now, though, there doesn't seem too much to worry about market access issues, even if the Phlow model works for the currently targeted supplies in the US, going by what some experts say. But "de-globalization" is likely here to stay and more protectionist measures may come in many markets, so spreading risk will be vital.

Ranjit Shahani, a former vice-chairman and managing director of Novartis India, said that, as a single company, Phlow, which also has "mixed heritage" and has only just started operations he noted, cannot impact India or China's "immense clout" for the moment. But perhaps for the first time in 50 years, the US government has "put a stake in the ground" and it's clearly a space to watch.

"It is not about one Phlow in the US but if there are other major countries in the developed markets who find this strategic move worth emulating that could be the 'thin end of the wedge' and could be cause for worry," Shahani, who is also president (emeritus) of the Organization of Pharmaceutical Producers of India, told *Scrip*.

COVID-19, the industry veteran predicted, will reshape the pharmaceutical supply chain for the future and mark a sharp "rebalancing" of where drugs and active pharmaceutical ingredients (APIs) are made, as countries recognize this as a key national security imperative. Currently, more than 80% of APIs and chemical ingredients used in the US to manufacture generics and over-the-counter drugs are produced abroad, the bulk of these coming from China and India.

NATIONS IN PROTECTIONIST MODE

Other experts in India underscored the value and optics involved in backing public benefit pharmaceutical manufacturing. Salil Kallianpur, a former executive vice-president at GlaxoSmithKline PLC in India who now runs a digital health consultancy, said that publicly-owned pharma firms like Phlow are quite obviously the "solution" for a country ravaged by both very high healthcare costs and COVID-19.

With the political leadership there battling an "image crisis", efforts to assuage the situation by offering manufacturing rights and support to a public benefit drug manufacturer like Phlow is a "good idea", he said.

"Even if it isn't about the political mileage, most nation-states are in protectionist mode with gradually reducing affection for globalization. This is probably a lesson for every country after global supply chains broke down with China shutting down briefly in the earlier part of 2020 [due to the pandemic]," Kallianpur told *Scrip*.

Deglobalization, the executive said, is something to worry about for all industry not just pharma and currently most large markets have realized the risk of over-dependence on China and are working hard to secure alternate sources of supply. India too has plans to ramp up production of APIs and become an alternative supplier for global drug makers hit by factory shut-downs in China.

"The Indian government has aggressively begun implementing a policy to ramp up local output and emerge as an alternate to China. The US seems to be doing the same thing," Kallianpur observed.

Indian companies that have a focused US market strategy should worry, he said, but those investing in diversification of products and markets have alternatives, "even if relatively less lucrative."

DRUG/VACCINE NATIONALISM

Other experts, however, suggest that US support for publicly-owned pharma manufacturing is more than just the "China factor" at play. Ex-CEO of India's Hilleman Laboratories, Dr Davinder Gill, described the trend as "drug or vaccine nationalism" in the context of the COVID-19 pandemic; typically, in this situation individual countries are trying to adopt nationalistic and protectionist policies towards their own citizens.

"Therefore countries are funding initiatives to secure essential drugs and medicines including vaccines for their populations. This particular step taken by the BARDA seems to be pointing in that direction," Gill told *Scrip*.

Phlow's up-front federal government funding of $354m is for advanced manufacturing of the "most essential" medicines at risk of shortage in the US, including medicines for COVID-19 pandemic response. Federal funds from BARDA, part of the office of Assistant Secretary for Preparedness and Response at the US Department of Health and Human Services (DHHS) have been deployed for the purpose.

Phlow's total contract value stands at up to $812m, including the initial four-year base award of $354m, plus $458m included as potential options for long-term sustainability.

There have been allegations of politicization of DHHS funding decisions, but for now the support has allowed Phlow, with assistance from its partners, to deliver 1.6 million plus doses of five es-

sential generic medicines used to treat COVID-19 patients to the US Strategic National Stockpile, including drugs for sedation, pain management and essential antibiotics.

Gill said that as such, the agreement between BARDA and Phlow does not cover the very large supply of generic medicines made by Indian pharmaceutical companies to the US. "I see this as a limited supply designed to meet emergency needs of severely ill COVID-19 patients," maintained the ex-chief of Hilleman, an equal joint venture between Merck & Co. Inc. and the Wellcome Trust.

BROADER ACCESS UNLIKELY TO BE HIT?

But as profitable markets like the US increasingly look inward for medicine supplies, does the Phlow-model put at risk the Indian generic industry's clout and market access plans? By some estimates, one in every three pills consumed in the US is produced by an Indian generics firm.

The US market is a significant contributor to earnings of almost all major Indian drug companies including Sun Pharmaceutical Industries Ltd., Dr. Reddy's Laboratories Ltd., Cipla Ltd. and Lupin Ltd., with analysts also highlighting that drug shortages in the US have at times contributed "handsome" earnings spikes for companies filling the gaps.

The Indian Pharmaceutical Alliance (IPA), which represents leading domestic firms, told *Scrip* that it was still trying to understand details of the new Phlow initiative, including plans for continuous advanced manufacturing processes, and how things may shape on the ground.

Consultant Kallianpur believes it's unlikely the Phlow model will affect broader market access plans for Indian firms given that most have invested heavily in creating differentiated portfolios (tech-transfer to public benefit companies is unlikely to happen, he noted) and are increasingly looking at an ex-US strategy to diversify risk.

"Even in the immediate term, Indian companies aren't probably vying for the pipeline of drugs that Phlow or others like them will be commissioned to manufacture," he explained.

Ex-Hilleman chief Gill similarly stated that there is breadth and depth in Indian companies supplying generics to the US and it could be "quite difficult to match the safety, quality and affordability of Indian pharmaceutical products sold worldwide."

FLOW CHEMISTRY

The industry experts also had interesting takes on Phlow and its partners' plans to use flow chemistry and other continuous advanced manufacturing processes under the initiative. The US collaboration said that the technology had not been widely adopted in the generic pharmaceutical industry, but that when used it can increase "the quality, safety, and volume of medicines, yielding lower costs for Americans."

Gill explained that "in reality", flow chemistry is not amenable to scale-up, adding that start-up costs can be high and often manufacturing plants have to be dedicated to a particular product. "So when it comes to the large number of generic medicines being supplied to the US, I do not see how companies like Phlow can compete with Indian pharmaceutical companies."

Kallianpur added another dimension, noting that Indian drug makers should perhaps be worried about the FDA asking US manufacturers like Phlow to adopt "continuous manufacturing" or creating smaller batches of medicines that need smaller scale, less labor, equipment and which can reduce quality problems.

"Indian manufacturers work on exactly the opposite scale, thereby escalating quality issues as we witnessed through the number of 483s issued. While these have reduced, they have not disappeared," the ex-GSK executive noted. A Form 483 is a notice of the FDA's inspectional observations that lists deficiencies in the quality system.

LEARNINGS FROM THE AUTO SECTOR?

While Indian drug makers maybe don't need to lose much sleep over the arrival of Phlow for now, Gill said there nevertheless are important lessons for companies.

The first, he emphasized, is to invest more in innovation and continuous improvement to ensure maintained supplies of safe, high-quality and cheap generic medicines worldwide. He also sees an opportunity for Indian companies to increase their investments, particularly in terms of local manufacture within the US, noting that decades ago Japanese and German automakers, in the face of similar "retaliation", ended up establishing production plants within the US.

"That model became so successful that the car makers replicated it in other countries including in India. Indian pharmaceutical companies can also set up manufacturing plants in the US to replicate this model," he suggested. Several Indian firms including Sun Pharma and Dr Reddy's already have sites in the US, though it remains to be seen if Phlow-like initiatives may influence their new investment plans.

The US generics trade association, the Association for Accessible Medicines (AAM), suggested in its recent "Blueprint for Enhancing the Security of the U.S. Pharmaceutical Supply Chain" report that guaranteed volume and price agreements are vital to ensure the viability of US-based generic manufacturing for high priority drugs.

Among a string of suggestions, the AAM also proposed that the US Trade Representative and the DHHS should negotiate a plurilateral agreement with allies to promote a cooperative approach to securing the US supply chain ensuring diversity of supply; allies such as Canada, Europe, India, Israel, Japan, Jordan and Mexico could be tapped. the blueprint proposed.

RIGHT OPPORTUNITIES TO KEEP INDIAN FIRMS GOING

Meanwhile, Kallianpur noted that India typically has a lower focus on APIs and bulk drugs and so the Phlow initiative and other similar moves will affect the Indian industry but "not knock it out." With India, through its "China plus one" strategy, seeking to revive interest in the pharma production sector, Indian manufacturers are capable of building economies of scale to make their products competitive in the US market, even with the likes of Phlow.

"Managing quality, focusing on making the right products and leveraging the right opportunities can keep Indian drug makers afloat," he believed.

But in a broader sense, in the finished formulations area, the Indian industry already "has its focus right" with differentiated portfolios and an ex-US diversification plan, the ex-GSK executive added.

Published online 26 May 2020

Novartis Joins Vaccine Efforts With Gene Therapy Approach

NOVARTIS'S AVEXIS TO COLLABORATE ON GENE-BASED VACCINE

Novartis AG has joined the industry-wide efforts to develop a vaccine against SARS-CoV-2, its AveXis division teaming up with a Massachusetts hospital on a gene therapy based candidate.

Its initial role will be limited to assisting in the manufacture of the candidate vaccine, but AveXis could exercise rights to develop and commercialize once it has advanced into mid-stage trials.

Clinical trials of the first gene-based vaccine against the novel coronavirus should start later this year. Its partners Massachusetts General Hospital and Massachusetts Eye and Ear announced on 28 May that the AAVCOVID vaccine is moving toward clinical studies, and on the same day Novartis AG's gene therapy unit AveXis Inc. signed on to help manufacture the adeno-associated viral (AAV) vaccine.

AveXis is contributing its expertise and manufacturing help at no cost. The company made its name developing Zolgensma, a AAV-based gene therapy for the rare disease spinal muscular atrophy, and believes it can help scale up the work of the New England hospital.

The AAVCOVID program comes out of the lab of Luk Vandenberghe of the Grousbeck Gene Therapy Center at the Massachusetts Eye and Ear. AAV is a well established gene therapy approach, and in the vaccine AAV will be used "to deliver genetic sequences of the SARS-CoV-2 Spike antigen so the body can develop an immune response to the coronavirus."

"AAV is a superior technology for safe and efficient gene delivery, and the unique technologies we are applying in AAVCOVID support the potential for a potent immunity to be induced to SARS-CoV-2 from a single injection," Vandenberghe said. "In a crisis, we can harness the power of molecular biology and develop a draft of a vaccine in weeks, and that's what was done here."

Based on the current animal testing, one or more candidates will advance for human tests. Once the first clinical trials are completed, the researchers aim to advance the study into later phases. AveXis will have the option to manufacture the AAV vaccine for additional clinical development, registration and/or commercial activities.

"The COVID-19 pandemic is the most urgent public health crisis of our time and we recognize the significance of evaluating the potential role of a gene-based vaccine," said Dave Lennon, president of AveXis.

"As one of the world's leading gene therapy companies, we are pleased to lend our unparalleled manufacturing expertise, technology and supply chain to produce a COVID vaccine for use in clinical trials. Having developed and produced one of just two, FDA-approved AAV gene therapies, we are uniquely poised to help the team move quickly toward this accelerated effort."

OXFORD BIOMEDICA TO MANUFACTURE ASTRAZENECA VACCINE

Oxford BioMedica PLC reported on 28 May that it has signed a one-year clinical and commercial supply agreement with AstraZeneca PLCto help the pharma company produce its adenovirus vector-delivered COVID-19 candidate, AZD1222.

In April, the two companies agreed to partner on global development, manufacture and distribution of the vaccine if it is approved. The new agreement gives AstraZeneca access to a new 7,800 square meter commercial manufacturing center in Oxford, UK.

THE AFTERMATH: ENGLAND OPENS SPECIALIST HOSPITAL FOR RECOVERING COVID-19 PATIENTS

As healthcare systems around the world are learning, patients who have been hospitalized with the most severe COVID-19 cannot simply return to normal life once they have been discharged from intensive care.

The coronavirus crisis has still not fully subsided in England, with the country still recording more than 300 deaths a day from the virus. Nevertheless, the National Health Service is now setting up dedicated services to deal with thousands of formerly critically ill patients who have recovered from the disease, but who have been left with long-term health problems.

NHS hospitals in England have provided inpatient and critical care for over 90,000 people with coronavirus over the last three months.

Some patients who have been admitted to intensive care wards can spent many weeks under sedation and intubated, and those who survive are often left with serious long-term problems, such as heart and muscle weaknesses which require co-ordinated rehabilitation.

Patients who emerge from sedation also suffer psychological problems, including "post-intensive care syndrome" and cognitive

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More Coronavirus Coverage

Coronavirus Update: Roche Launches Remdesivir Plus Actemra Trial, GSK Plans 1 Billion Vaccine Adjuvant Doses: https://bit.ly/3ctBuAN

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CONTINUED FROM PAGE 16

impairment, and many of these will also need help with washing and dressing in order to return to their homes.

The NHS in England has just opened its first hospital dedicated to caring for these patients, The Seacole Centre at Headley Court in Surrey. The hospital is named in honor of the pioneering nurse Mary Seacole, and will provide specialist rehabilitation care for patients who are recovering from COVID-19 in the Surrey region, with more specialist units to follow nationally.

Local NHS teams will work with counterparts in local councils and voluntary groups to expand community provision to create for these patients integrated packages of care at home and in the community.

The services aim to speed the recovery of patients by bringing together a wide range of specialist staff, including doctors and nurses but also mental health staff, pharmacists, dieticians, speech therapists, physios, occupational therapists, psychologists and social workers. Each local area is being asked to plan how best to deliver services, while maintaining increased critical care capacity, as the risk of a second wave of infections remains high.

Meanwhile the impact on patients with other health conditions which have not been treated during the period is also yet to be fully understood. To help restore these services, the NHS is being asked to bring back non-urgent services on a phased basis including routine tests and operations.

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China's New Hong Kong Security Law To Derail Biotech IPOs?

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On 28 May, China's National People's Congress overwhelmingly passed a new National Security Law for Hong Kong, which many see as a potential curve ball to many aspiring biotechs from the mainland hoping to raise funds through an initial public offering in the international finance hub.

For many health startups and especially biotech firms constantly on the look out for global deal-making, the charms associated with Hong Kong include its relaxed economic controls, proximity to mainland China and a currency pegged with the US dollar, making it hard for Chinese cities such as Shanghai and Shenzhen to compete.

But with the new law and looming possible sanctions from the US, which is reconsidering the special status given to Hong Kong post-1997 when it was handed back to China by the UK, many see the sudden changes as potentially impacting corporate decisions over where to list shares.

The US special status permits Hong Kong to enjoy tax rates more favorable than the tariffs levied on goods from mainland China and zero tax on goods from the city has largely protected it from any impact from the now years-long US-China trade war.

Hong Kong is also an established financial center for companies looking east and also Chinese firms eyeing the global market, after years of economy prosperity and trading with countries all round the world.

SECOND-LARGEST BIOTECH IPO CENTER

The biggest draw of Hong Kong is this "East-Meets-West" environment, which many see as providing a springboard to China and a bridge from China to the world. As many as 1,200 US corporations have set up a presence in the city and more Chinese firms are courting international investment by establishing Hong Kong offices.

New China national security law to affect Hong Kong IPOs?

As Hong Kong is increasingly looking to a burgeoning China to drive growth, its Stock Exchange (HKEX) in March 2018 revamped listing rules to allow pre-revenue companies to pursue an IPO. Soon, many biotech startups showed interest, including novel drug developers but also medical device firms and bioscience service providers.

For many company founders, a HKEX listing provides a combination of international finance market rules with a close-to-home appeal, which is particularly strong for bioventures courting the Chinese domestic market for their new drugs - the so-called "In China for China" development strategy.

Additionally, a linkage between the Hong Kong, Shanghai and Shenzhen stock markets, China's two major financial centers, gives domestic investors easier access to Hong Kong-traded stocks.

It's thus not surprising that by last September, HKEX reported that 16 biotechs had listed there, raising HK$53.5bn ($6.9bn) in total. More than half of these were pre-revenue firms under the relaxed listing rules, noted the exchange. With varied companies joining the party, Hong Kong is now ranked as the second-largest fundraising center for biotech, after Nasdaq in the US.

In just the February-September period last year, nine biotechs listed their shares, ranging from oncology developer CStone Pharmaceuticals Co. Ltd., to vaccine group Tianjin CanSino Biotechnology Inc. and contract research firms such as Viva Biotech and Frontage, biosimilar developer Shanghai Henlius Biotech Inc., Jiangsu Hansoh Pharmaceutical Group Co. Ltd., Mabpharma and devices company IVD Medical.

Entering 2020, the queue continued. Immuno-oncology developer Akeso Pharmaceuticals became the latest to get a listing and many others such as orphan drug developer CANbridge Life Sciences Ltd. have shown interest.

UNCERTAIN FUTURE

Now that China appears to be further tightening its grip over Hong Kong via the new security law - which would make undermining Beijing's authority a criminal offence in Hong Kong - many see that biotech IPO plans may see some adjustment.

Whether Hong Kong will remain the international finance hub as many hope will hinge in part on the US decision over special status; the US State Department has said it can no longer certify the requisite "autonomous status" for Hong Kong. Meanwhile, Beijing's muscle-flexing rule is also causing concern among investors who are casting doubt over the city's continued appeal to foreign investors, especially from the US.

At present a wait-and-see attitude is being adopted by many, who will be closely watching how China will impose the law. Intended in the mainland's view to bring stability to the city, which has been riven by pro-democracy protests, the law will likely take effect in late June and would punish those considered to be engaged in "secession, subversion, terrorism and foreign interference."

Throughout 2019, the city saw waves of protests across its streets and shopping centers, some violent, and China is seemingly determined not to allow a repeat. But the passing of the current law by China, without the involvement of Hong Kong's own Legislative Council, could also damage the city's global standing and image in the business arena, some say.

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CVS Warns Broader Cost Controls Coming As Economic Downturn Collides With Costly New Therapies

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Pharmacy benefit managers are looking at redoubling efforts to control prescription drug costs in response to payer concerns with financial pressure from the pandemic-driven economic downturn combined with growing numbers of high-cost cell and gene therapies entering the US market, according to CVS Health Corp.'s Caremark president Alan Lotvin.

It's "unquestionable" that payers are increasingly interested in establishing stronger controls on drug utilization and cost in the months and years ahead, he said during a webinar sponsored by the Pharmaceutical Care Management Association on 20 May.

"We've started to see early signs of that, people already saying, 'OK, I got it. The world has changed. We've gone from a 3% unemployment [rate] to 14% and now I'm worried about affordability,'" Lotvin reported.

As a result, "we've certainly seen increased interest in more comprehensive management solutions that we [PBMs] bring to bear" such as formulary exclusions and increases in utilization management like prior authorization, he maintained. His comments echo other reports that in the coming months, payers will refocus attention on controlling drug costs as a result of the financial stress caused by the pandemic.

He also expects "we will continue to see questions from clients that get to the very heart of coverage: 'What do I absolutely need to cover and why do I have to cover it?'" CVS has "certainly heard people ask, 'Can I wholesale exclude classes?' not as a formulary discussion…but as a plan design discussion. So just from a plan design perspective, 'Why do I need to cover category X or why do I need to cover type of agent Y?'"

For a relatively small, self-insured company, "some of the new agents, particularly extraordinarily high-cost agents…could represent their entire earnings for the year. So that becomes an existential threat," he pointed out. "What we have to do as a PBM industry is to create headroom for innovation from pharma. There are not unlimited budgets…In order to get to the new innovations, we have to take down the costs of older drugs."

TIME WILL TELL HOW MUCH INSURERS FEEL THE PINCH

Reimbursement/health policy consultant and former US Health and Human Services Department senior advisor John O'Brien believes it is "too soon to tell" how much financial stress insurers will feel and whether they will resort to excluding whole categories or types of agents from coverage.

"For the last three months I've been saying insurers haven't spent a nickel on anything except COVID since February," he said in an interview. They may lose premium revenues as employers go out of business, drop coverage or furlough employees, he noted. But their spending has also been lower because members have avoided non-COVID medical care.

O'Brien is not surprised PBMs are seizing this chance to say that with high unemployment, "everybody's got to tighten their belts and that's what we do, help them tighten their belts." He also predicted "they're probably going to over-correct a little bit and use this as an opportunity to squeeze as much as they can from manufacturers."

However, "my hope is that if PBMs do their jobs well, they will not likely need to exclude whole classes of drugs and no employer will ever have to say 'We're not going to cover treatments for rheumatoid arthritis' or 'We're only going to cover methotrexate for rheumatoid arthritis.'"

REINSURANCE, RISK POOLING SOLUTIONS

O'Brien also expressed confidence that payers will figure out ways to pay for gene therapies. He predicted reinsurance solutions "will continue to gain ground" and that insur-

ers will look toward pooling risk to cover high-cost treatments.

PBM Prime Therapeutics and BCS Insurance announced a new reinsurance program called PreserveRx for cell and gene therapies in early April. Offered to Blue Cross Blue Shield plans, PreserveRx will initially provide financial protection for two gene therapies on the market: Roche's Luxturna (voretigene neparvovec-rzyl), which treats an inherited form of blindness, and Novartis AG's Zolgensma (onasemnogene abeparvovec) for spinal muscular atrophy.

Prime also expects it will cover three upcoming gene therapies. They include BioMarin Pharmaceutical Inc.'s Roctavian (valoctocogene roxaparvovec) for hemophilia A (a decision on US approval expected in August), PTC Therapeutics Inc.'s GT-AADC for aromatic L-amino acid decarboxylase deficiency (US application expected to be filed in the second half of 2020), and bluebird bio Inc.'s LentiGlobin for beta thalassemia (completion of a rolling application in the US expected in mid-2021).

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'Friendly Breakup': Sanofi And Regeneron Agree Equity Revamp

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In a mutually agreed set of stock transactions, Sanofi will offload most of its 20.6% stake in Regeneron Pharmaceuticals Inc. while the US pharma will buy much of it back as part of CEO Paul Hudson's plan to generate cash and re-vamp the French drug maker. Both said the coordinated equity exercise would not hurt their successful and lucrative drug development partnership.

The two companies have had a research and marketing partnership since 2003, which led Sanofi to build up an equity stake currently worth around $12bn. But last December, newly installed CEO Hudson hinted during a presentation to investors that Sanofi would "monetize" its Regeneron stake as part of a necessary overhaul that included the Paris-based group exiting diabetes R&D and a re-ordering of therapeutic priorities, to spur growth.

Sanofi currently holds around 20.6% of Regeneron shares outstanding or 23.2 million shares. The French group is offering 12.8 million shares in a public offering and has granted the underwriters an option to purchase up to an additional 10% of Regeneron's shares offered, exercisable within 30 days following the pricing of the offering.

Regeneron said it would buy around $5bn of the shares offered, which analysts calculate to currently be around 8.7 million shares, using $3.5bn from cash-on-hand and $1.5bn in bridge financing.

If the offering and repurchase are completed and the underwriters fully exercise their option to purchase additional shares, Sanofi will continue to own approximately 400,000 shares of Regeneron's common stock, which Sanofi in a statement said it "is retaining in support of the ongoing collaboration with Regeneron."

> "We believe the proceeds from this transaction will help further our ability to execute on our strategy to drive innovation" - Paul Hudson, Sanofi CEO

Sanofi boss Hudson said that the money generated from the Regeneron equity exit would go towards boosting the French group's research and development of new drugs, and could include acquisitions.

"Sanofi and Regeneron's collaboration has been one of the most productive in the industry, creating significant value for both companies but more importantly, resulting in five important medicines for patients," said Hudson, who took over the top spot at Sanofi in August 2019, succeeding former CEO Olivier Brandicourt. *(Also see "Sanofi's New CEO Paul Hudson Poised To Write The Next Chapter" - Scrip, 1 Oct, 2019.)*

LUCRATIVE PARTNERSHIP

Hudson said Sanofi remained committed to continuing its collaboration with Regeneron, and that "it remains an integral part" of Sanofi's overall future strategy.

"This decision was fully aligned with Regeneron. The decision to divest our holdings is consistent with our efforts to enhance value creation for our shareholders. We believe the proceeds from this transaction will help further our ability to execute on our strategy to drive innovation and growth," Hudson explained.

The duo has had a successful and long-standing clinical and commercial collaboration dating back to 2003 that has resulted in five approved treatments to date with additional candidates currently in clinical development. Sanofi originally purchased a shareholding in Regeneron in 2004.

During that long-standing alliance, Regeneron has blossomed into a pharma player that is widely known for its antibody drug development platform and commercial success with Eylea (aflibercept) but is also increasingly moving towards the therapeutic area of oncology. It has one cancer drug on the market, the PD-1 inhibitor Libtayo (cemiplimab) in partnership with Sanofi, but behind it are a maturing pipeline of bispecific antibod-

ies that Regeneron hopes will allow it to evolve into a major oncology player.

On 5 May, Regeneron and Sanofi announced positive top-line results from a single-arm, open-label, Phase II study evaluating Libtayo in patients with advanced basal cell carcinoma, the most common type of skin cancer. Regulatory filings are expected during later this year.

That same day, Regeneron posted robust revenue growth in this year's first quarter and said it was moving an antibody cocktail for treating COVID-19 into clinical testing. *(Also see "Regeneron Maintains Its Momentum During Pandemic" - Scrip, 5 May, 2020.)*

Dupixent (dupilumab), Sanofi's interleukin-4 and 13 inhibitor which is partnered with Regeneron was recently described as "the star in Sanofi's portfolio" by its R&D head John Reed.

FRIENDLY BREAKUP

Analysts applauded the announced coordinated equity transactions, saying the arrangement removed uncertainty in the market which had been clouding Regeneron's stock price.

Credit Suisse in a note to investors dated 25 May said, "This is the removal of a key overhang for Regeneron shares."

"The path to Sanofi unwinding its position in Regeneron is clear and will be done in an orderly process. Investors can now focus on Regeneron's fundamentals, which we maintain are strong, and not worry that Sanofi would dump shares after the December 2020 lock-up expiration [agreed in 2014 by the duo regarding Regeneron's common stock owned by Sanofi]," they explained.

"It is only a 'break-up' in Sanofi's ownership stake in Regeneron. The two companies appear to remain committed to the success of Dupixent and Libtayo and will continue to work collaboratively on the development and commercialization of these assets," Credit Suisse concluded.

Analysts noted that Sanofi can use the remaining 400,000 Regeneron shares that it will still hold to cover R&D funding commitments, which amounts to $50-60m per quarter, but other than using that stake to pay Regeneron for such services rendered, the stock remains locked-up until December 2020.

Published online 26 May 2020

Stockwatch: The Victimization Of Big Biotech

ANDY SMITH

Less than a month after its first-quarter earnings release, Alexion Pharmaceuticals Inc. held a post-earnings corporate update call. For a stock that had until the update, significantly underperformed the NASDAQ Biotech Index (NBI) in the year to date, perhaps it was understandable that Alexion would want to redress that imbalance. However, for biotech companies that have tasted spectacular product success, repetition remains a most difficult second act.

ALEXION TREADS WATER

When Alexion reported its first-quarter 2020 financial results in early May, its stock price finished the day down 1.4%. This added to the previous day's 5.4% drop after it announced the $1.4bn acquisition of Portola Pharmaceuticals Inc. In the year prior to its end of May update, Alexion's stock price had fallen by 6.5%, underperforming the NBI, which had risen by 10.3%.

Alexion's first-quarter report was, however, almost uniformly positive with total revenues of $1.44bn and non-GAAP earnings per share (EPS) of $3.22 growing 27% and 35% respectively, over the same period in 2019. Revenue and non-GAAP EPS both beat analysts' consensus estimates. Alexion's total revenues grew by 4.4% sequentially from the fourth quarter of 2019 and remain dominated by its largest and first approved product – Soliris (eculizumab) for hematological indications including paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). Soliris's more than 70% of Alexion's first-quarter revenues grew 6.3% over the same period in 2019 and 1.0% from the fourth quarter of 2019. In many ways Alexion is a victim of Soliris's success, since not only has it taken the US market's most expensive drug and expanded it into additional orphan indications, but it has found repeating the drug's success a most difficult challenge.

The stock price drop after Alexion's first-quarter earnings report was probably due to its lowered guidance as a result of the coronavirus pandemic that had "slowed new patient initiations and delayed treatment starts." Alexion's revised guidance lowered total revenues and non-GAAP EPS by 4.5% and 1.4% respectively, at the mid points. Alexion should have been applauded for its transparency in territory that bigger companies like AstraZeneca PLC and Roche have feared to tread. If an orphan drug company whose products are prescribed and administered by specialist, clinic-based physicians can recognize the pressures on financial guidance that the coronavirus pandemic has brought, it seems that pharmaceutical companies with heavy weightings in clinic-prescribed and administered (oncology) products may be saving up shock guidance reductions as uncomfortable surprises for their investors.

VICTIMS OF FIRST PRODUCT SUCCESS

Alexion is not alone in being a big biotech company with a hugely successful first product. This brings growing pains that Amgen Inc. and Gilead Sciences Inc. also have experienced. Indeed, investors, being an unforgiving lot, are rarely content with the success of one product when its loss of exclusivity appears on the horizon. If investors can't see a repetition of the same upside to revenue and earnings that the first product conveyed, stocks can enter that twilight zone before patent expiry where revenues and earnings still grow, but the share price falls. Investors' reduced expectations are reflected in a lower price to earnings ratio (PE ratio) than the average biopharma company. Before the coronavirus pandemic spread out from Asia in February, the PE ratio of Alexion was 10.7 against a US biopharma average of 17.5. Alexion's PE multiple partly reflects investors' concerns of biosimilar

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Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

Click here for the entire pipeline with added commentary: http://bit.ly/2mx4jY3

PIPELINE WATCH, 22–28 MAY 2020

PHASE III

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Gilead Sciences, Inc.	remdesivir	COVID-19	ACTT (NIAID); NEJM, 22 May, 2020	0	71
Phase III Updated Results	Genmab/Johnson & Johnson	Darzalex Faspro (daratumumab)	Amyloid light-chain Amyloidosis	ANDROMEDA; Met Primary Endpoint	0	62
Phase III Top-Line Results	Sanofi/Regeneron	Dupixent (dupilumab)	Eosinophilic Esophagitis	Met Co-Primary Endpoints	5	64
Phase III Top-Line Results	argenx N.V.	efgartigimod	Myasthenia Gravis	ADAPT; Achieved Primary Endpoint	4	68
Phase III Top-Line Results	Roche Holding AG	ranibizumab PDS	Wet Age-Related Macular Degeneration	Archway; Positive Results	0	55
Phase III Trial Initiation	Roche/Gilead	Actemra (tocilizumab)/remdesivir	Severe COVID-19 Pneumonia	REMDACTA; In Hospitalized Patients	0	61
Phase III Trial Announcement	Boehringer Ingelheim/Lilly	Jardiance (empagliflozin)	CHF Prevention Post-MI	EMPACT-MI; With and Without Diabetes	0	47

PHASE II

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase IIb Updated Results	Merck KGaA	evobrutinib	Multiple Sclerosis	OLE, vs. Tecfidera; Sustained Efficacy	0	52
Phase II Updated Results	Zynerba Pharmaceuticals, Inc.	Zygel (cannabidiol) gel	Seizure Disorders	BELIEVE 1; Encouraging Results	0	19
Phase II Updated Results	Iovance Biotherapeutics, Inc.	lifileucel cell therapy	Melanoma, Advanced	innovaTIL-01; Positive Results	0	15
Phase I/II Updated Results	Aeglea BioTherapeutics, Inc.	pegzilarginase	Arginase 1 Deficiency	101A, 102A; Durable Responses	0	64

Source: Biomedtracker, company reports. LOA: Biomedtracker's opinion on likelihood of approval.

CONTINUED FROM PAGE 21

competition to Soliris from Amgen in 2021, and the emergence of a competitive product from Roche. *(Also see "Roche Mounts NMOSD Challenge To Alexion's Soliris" - Scrip, 12 Sep, 2019.)*

There are at least two ways a biopharma company can help its investors recognize that its future earnings growth could be higher than their expectations – the development of follow-on products and making sensible acquisitions without overpaying – and in fairness to Alexion, it has tried both. Alexion's follow-on product to Soliris is Ultomiris (ravulizumab), a longer-acting version of Soliris which was approved by the FDA in 2018 for PNH and in 2019 for aHUS. Even though it was launched at a list price discount to Soliris and found to be non-inferior in clinical studies, Ultomiris has a tough job to increase its first-quarter sales of $222.8m or 15.4% of total revenues, nearly two years after launch.

M&A PROVIDES NO ESCAPE FROM AN INITIAL SUCCESS

Alexion's non-organic route to diversifying and replacing Soliris's revenues before Amgen's biosimilar launch has also proven a challenge. Its first skirmish into the acquisition arena ended in the disaster now known as Synageva BioPharma Corp. The cost of the Synageva acquisition has now largely been written down although the combined $198.9m in Strensiq (asfotase alfa) and Kanuma (sebelipase alfa) revenues, or 13.6% of Alexion's total, lingers as an uncomfortable reminder of their $8.4bn cost. If Synageva was the worst of Alexion's seven acquisitions, which have cost $12.7bn in initial payments alone since 2011, its lower than average PE ratio and the acquisitions' minor contribution to its first-quarter revenues probably explain investors' less than diplomatic reaction to Alexion's most recent acquisition of Portola. Portola's first-quarter revenues were $25.6m, up from $22.2m in the same period in 2019, and it is therefore to be expected that an activist investor has openly criticized the transaction.

So, it was not surprising that Alexion held its late-May update call to bolster its investment case with analysts and investors, and to defend its acquisition of Portola. A cursory glance at the year-to-date stock price performance of Alexion against the NBI after the call would seem to support that the objective was achieved. Alexion's underperformance had been reversed by the end of the week into a 1.2% outperformance and a PE ratio of 11.3. That is, until you realize that the turnaround started hours before the update call with a 7.6% premarket jump on news leaking of a "settlement agreement in principle" with Amgen that would appear to delay its biosimilar Soliris launch. Sometimes there is no escape from the swings and roundabouts of that elephant of first product success.

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Andy Smith gives an analyst and former investor's view on life science companies. He joined the independent research house Equity Development in October 2019 having previously been an analyst at Edison group and a Senior Principal in ICON PLC's Commercialization, Pricing and Market Access consulting practice. Smith has been the lead fund manager for four life science–specific funds, including 3i Bioscience, International Biotechnology and the AXA Framlington Biotech Fund. He was awarded the techMark Technology Fund Manager of the year for 2007 and was a global product manager at SmithKline Beecham Pharmaceuticals until 2000.

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Tara Heitner	Cyxone AB	Chief Executive Officer	ISD-Immunotech	Chief Executive Officer	1-Jun-20
Douglas E. Feltner	Exicure	Chief Medical Officer	AveXis	Vice President, Clinical Development	18-May-20
John Ohd	Karolinska Development AB	Chief Scientific Officer	Modus Therapeutics	Chief Medical Officer	18-May-20
William Erhardt	Oligomerix Inc	Chief Medical Officer	Pfizer Inc	Senior Vice President and Head, Clinical Development Operations	19-May-20
John S. Sundy	Pandion Therapeutics	Chief Medical Officer	Gilead Sciences	Senior Vice President, Inflammation Therapeutic Area Head	19-May-20

Click here for all appointments: https://bit.ly/2oHWRYn

Source: Medtrack | Informa, 2020

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