Breathing easier with combinations

The first approved combination therapy against cystic fibrosis will open up an increasing proportion of patients for treatment. As Anna Azvolinsky reports, companies are banking on it.

The first drug to target the most common genetic defect of cystic fibrosis was approved in July 2015 by the US Food and Drug Administration (FDA). The new drug, Vertex's Orkambi, can treat as many as half of cystic fibrosis patients. Orkambi combines Vertex's first approved cystic fibrosis drug, Kalydeco (ivacaftor), with a second small molecule, lumacaftor. Both molecules attack the root cause of the disease—a mutated cystic fibrosis transmembrane conductance regulator (CFTR) protein, which shuttles ions across epithelial cell membranes—rather than treating symptoms.

"Being able to treat the underlying cause of the disease in so many patients is exciting, it's something we have never done before," says Brian O'Sullivan, former director of the cystic fibrosis center at the University of Massachusetts Children's Medical Center in Worcester.

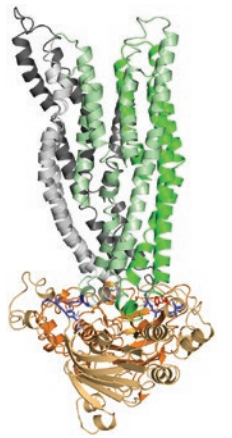
Orkambi was designed for those patients with two copies of the most common cystic fibrosis mutation, the F508 deletion (F508del), who make up about 50% of the cystic fibrosis population, or ~8,500 patients. Yet, the therapy is not a boon for patients, who still rely on their symptom-alleviating tool kit of physical therapies, inhaled medications, antibiotics and diet modifications. Unlike the substantial improvement in lung function patients receive from Kalydeco, the clinical benefit of Orkambi is modest. But its approval is seen as an important proof of concept for other combination therapies that will provide greater relief for F508del patients.

Homing in on CFTR

January 2012 marked a turning point in the treatment of cystic fibrosis; the FDA approved Kalydeco, the first drug targeting the protein that causes cystic fibrosis, from Boston-based Vertex Pharmaceuticals. Whereas all previous therapies treat only symptoms or control potentially deadly lung infections, Kalydeco directly modifies mutated forms of the CFTR protein. Called a potentiator, Kalydeco is thought to bind directly to the CFTR protein, boosting the frequency with which the channel opens and closes and the length of time the channel stays open, thereby boosting chloride transport (**Box 1**).

The drug initially was approved for the 4% of patients with the G511D mutation (~1,200 patients in the US), one of hundreds of mutations in CFTR that cause the genetic disorder (*Nat. Biotechnol.* **30**, 201–202, 2012). The label has since been expanded to include nine additional mutations, yet these genetic alterations still account for only ~2,000 patients out of the 30,000 in the US.

Orkambi combines Kalydeco with a so-called corrector molecule, lumacaftor, which counteracts a CFTR folding defect caused by the F508del mutation and facilitates proper folding of the protein as it is being synthesized (**Box 1**). In two phase 3 trials of >1,000 patients—the largest yet conducted for cystic fibrosis—Orkambi treatment led to a modestly increased lung function of 2.6–4.0%, as measured by forced expiratory volume in one second (FEV1)—in patients taking the combination, compared with those on placebo. In contrast, Kalydeco had a more substantial, approximately 10% lung function benefit. "Patients on Kalydeco therapy have a clear benefit in lung function, often saying they feel better," says Michael Boyle, the director of the adult cystic fibrosis program at Johns Hopkins University (Baltimore) and lead author of the two Orkambi studies. Patients who took part in the Orkambi phase 3 trials saw a smaller benefit, and most patients could not sense a difference in their daily life, although according to Boyle, some patients were able to do exercise, which they were unable to do prior to starting on the drug.



Protein data base rendering of CFTR. Reprinted from *Nat. Chem. Biol.* **9**, 444–454, 2013).

"The change in pulmonary function was positive but not dramatic," says O'Sullivan. "This is not the endgame, we still need something better." Boyle agrees. "The key here is to…continue to get more and more potent therapies," he says.

What was notable in the Orkambi trials, according to Boyle, was the meaningful reduction in pulmonary exacerbations. The rate of pulmonary exacerbations was 30–39% lower in the Orkambi treatment group than the placebo group. With the combination there were also fewer hospitalizations and less frequent need for intravenous antibiotics than with placebo. The effect of the drug combination was also consistent across subgroups, such as younger and older patients, those with a relatively low FEV1 at screening and those infected with *Pseudomonas aeruginosa*, a major cause of lung infections in cystic fibrosis patients. "It was actually comforting for us to see that there was a consistent, across-the-board benefit," says Boyle.

Orkambi, like Kalydeco, was tested in patients whose baseline FEV1 was at least 40%. Although its use is not restricted from use those with more advanced lung disease, Vertex is now running a phase 3b study to test whether Orkambi is effective in homozygous F508del patients with more advanced lung disease, with a FEV1 of <40%. A safety study of the combination in children between the ages of 6 and 11 is also under way and expected to be completed and submitted to the FDA in 2016.

Expanding the patient pool

Vertex is already working towards improved therapies, combining Kalydeco with novel small molecules in two-drug combinations, and has plans to start testing a three-drug combination. In total, the company's ongoing and planned clinical trials would capture about 90% of all cystic fibrosis patients. Currently in clinical testing is another Vertex corrector, VX-661. This molecule is chemically similar to lumacaftor but behaves differently *in vivo*. Lumacaftor interacts with Kalydeco, reducing the level of Kalydeco in the blood, and necessitating a higher dosage of Kalydeco, which makes the combination less than ideal. VX-661 does not share that property and is being tested in four phase 3 trials, including one in combination with Kalydeco in patients heterozygous for the F508del mutation, who also have a second Kalydeco-responsive mutation. "Vertex wants to raise the efficacy bar in Kalydeco-treated patients, to make it harder for competition to penetrate the market," says Michael Yee, an analyst at investment bank RBC Capital Markets in San Francisco.

Another phase 3 trial of VX-661 plus Kalydeco in patients with one F508del copy and a second minimal function CFTR mutation has just begun and is expected to be completed in 2016. These heterozygous patients comprise 20–30% of all patients who currently are ineligible for either Orkambi or Kalydeco. But analysts including Yee and Phil Nadeau of the New York–based Cowen Group are skeptical that the duo combination will work in this patient

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Box 1 Folding and opening

CFTR—discovered in 1989 by Lap-Chee Tsui and John Riordan, of the University of Toronto and Francis Collins' group at the University of Michigan—encodes an ATP-binding transporter class ion channel, selective for chloride ions, that is embedded within the membrane of epithelial cells in the lungs, pancreas, skin and the gastrointestinal tract. The protein allows chloride ions to shuttle back and forth across cell membranes. Along with the balance of sodium ions across the membrane, regulated by specialized sodium channels, chloride ion movement is needed to produce lubricating mucus in the epithelial cells of the lungs, secretion of digestive enzymes in the digestive tract, and sweat in the skin. An imbalance of the ions due to faulty channel function or too few channels creates abnormally thick and tacky mucus that blocks bronchi function, resulting in frequent chest infections. Because most patients have lung complications and ultimately die of respiratory failure, drug developers have focused on lung function as a measure of efficacy. Yet, because CFTR-targeted therapies are systemic, they may also improve other organ function, according to researchers. Kalydeco, for example, results in substantial—and beneficial—weight gain in patients partly because the contents of the digestive tract become less acidic, allowing for better nutritional absorption.

Two kinds of mutations underlie cystic fibrosis. One type results in fewer channels at the cell surface due to defects in protein translation and folding. The second comprises gating mutations that allow the channels to get to the cell surface but the channels have trouble opening and closing, leading to poor chloride ion transport. Mutations can cause more or less dysfunction, but the type of mutation does not necessarily dictate the severity of disease. The more severe cystic fibrosis mutations cause earlier disease onset and more rapid compromise of lung function, due to thick mucus, along with malfunction of other affected organs. "Some gating defects, [such as the G551D mutation] treated by Kalydeco, can result in as severe a disease phenotype as those where no CFTR makes it to the cell surface," says Paul Negulescu of Vertex.

Because cystic fibrosis is caused by malfunction of a single protein, the push in drug discovery has been to restore the malfunctioning CFTR protein, a particularly tall order. Most small-molecule therapeutics block the function of a mutated protein; finding compounds that enhance protein function is trickier because it requires understanding not only the protein's structure and function at the molecular level but also how it behaves in the cellular context. CFTR is a particularly difficult target to boot, according to Gergely Lukacs, of McGill University, who studies CFTR, because the protein is intricate with five domains, two of which traverse the cell membrane several times, making it difficult to fold, even in its nonmutated form. To fully restore CFTR function, stability defects in several domains would need correction, and to date, molecules that can do that have not been found.

The normal channel must bind to ATP to open, but can also open, although rarely does, without any ATP present. "What Kalydeco seems to do is enhance this rare but naturally occurring form of gating," says Negulescu. Because many CFTR mutations occur around the ATP-binding site, this mechanism of action may also explain why Kalydeco can work on a spectrum of mutant CFTR forms.

The second drug in the Orkambi combination, lumacaftor, is known as a corrector molecule. The drug is thought to bind to CFTR during synthesis, to facilitate its folding before it reaches the cell surface. In patients with the F508del mutation, the mutant protein, because it is not processed properly, rarely reaches the cell surface.

With F508del patients, both a corrector and potentiator are needed because the mutation decreases the number of channels that can fold properly in the cell, and the few that are able to reach the cell membrane do not work well. "Lumacaftor helps to improve the processing of CFTR, allowing trafficking to the cell surface where Kalydeco boosts its function," explains Negulescu.

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group. "In the phase 2 trial, [VX-]661 plus ivacaftor [lung function improvement] was similar to that seen with Orkambi. Because of that, I don't think the new combination will be potent enough to work in [F]508del heterozygous patients," says Nadeau.

Rather, analysts are looking forward to a second-generation corrector from Vertex, which binds to a different region of the CFTR protein than either VX-661 or lumacaftor, providing greater stability during its assembly. Vertex recently announced that two such correctors, VX-440 and VX-152, would enter the clinic in November. The company expects to use the Kalydeco plus VX-661 combination as a foundational regimen to which they will add one or two additional correctors. "We think VX-661 is a better candidate for triple combos, which is our current big push," says Paul Negulescu, senior vice president of research at Vertex's San Diego site. The triple combination for heterozygous F508del patients represents a potential $1-billion to $3-billion opportunity, according to Yee. Pending the initial second-generation corrector trial results, triple combination trials in F508del homozygous and heterozygous patients will begin next year. If Vertex's combinations—either VX-661 plus Kalydeco or the triple combination—are approved for this heterozygous population, this could expand the treatment-eligible patient pool to as high as 90%.

According to Gergely Lukacs, professor of physiology at McGill University in Montreal, correctors that rescue the F508del with high efficiency will be extremely important for heterozygous patients. Finding efficacious molecules for each rare mutation will be more challenging, he says. "The ultimate goal is to find a second corrector that will complement VX-661. It comes down to the basic folding repair of the molecule. Through his structural studies, Lukacs has shown that targeting at least two critical points in CFTR can boost the protein's function by synergistically rescuing the folding defect (*Nat. Chem. Biol.* **9**, 444–454, 2013).

In June, Vertex announced a collaboration with Parion Sciences of Durham, North Carolina, to develop a drug against another target in cystic fibrosis, epithelial sodium channels, overactivation of which is "another effect of CFTR not working," says Boyle. The two companies plan to begin a combination trial of Parion's sodium channels inhibitor (currently in phase 2b as monotherapy) plus Orkambi in early 2016. Normally, the CFTR protein down-regulates sodium channels, but without functional CFTR proteins, the sodium channels pull too many sodium ions out of the airways, exacerbating the already dehydrated bronchi. "Fixing the chloride channel and turning down the sodium channels could, together, potentially be synergistic to rehydrate the airways," says Boyle.

Although Vertex has a clear lead, other biotech and pharmaceutical companies are developing agents to grab a piece of what analysts estimate to be an $8-billion market. Mechelen, Belgium–based biotech Galapagos, in partnership with AbbVie of Chicago, presented the first clinical data on its potentiator, in healthy volunteers, in October. "[Our potentiator] binds

differently to CFTR than Kalydeco, and we can generate a higher response rate *in vitro*," says Galapagos CSO Piet Wigerinck. "Now we need to see if that will translate to a better efficacy." The company also has a corrector molecule that they say will soon enter trials and is looking to select a second corrector by the end of this year. Like Vertex, Galapagos wants to develop a triple combination that can target multiple CFTR mutations to more than double the current efficacy of Orkambi, says Wigerinck.

Other companies with CFTR-targeting small molecules in early-phase clinical testing include Lexington, Massachusetts–based Concert Pharmaceuticals, which is testing a deuterium-modified Kalydeco, and Flately Discovery Labs, which has a corrector in phase 1 trials.

A pretty penny

The excitement over Orkambi and Kalydeco has been partly tempered by their hefty price tags. Kalydeco costs more than $300,000 per year and Orkambi, $259,000. "As a doctor I am thrilled that we have Orkambi for patients but I worry how the healthcare system will accommodate it," says Richard Moss, a pediatric pulmonologist at the Lucile Salter Packard Children's Hospital at Stanford University in Palo Alto, California. Although the price is high—especially for a therapy that patients expect to take throughout their lives—Moss and other clinicians say they begin both eligible asymptomatic and symptomatic patients on the regimen. "The goal of these therapies is to start them before there is lung damage," says Boyle. "Kids that start these drugs before they have scarring in their lungs may not need to take a lot of their other medications and may not end up with other systemic problems."

Although the adult Orkambi phase 3 study demonstrated a reduction in disease exacerbations that led to hospitalizations, clinicians are skeptical that even with just one annual hospitalization, that the medications are cost-effective. O'Sullivan, who along with clinical colleagues, published an editorial on the high price of Kalydeco, says the price of Orkambi is "unconscionable" (*JAMA* **310**, 1343–1344, 2013). "Orkambi has a modest efficacy but not a modest price," he says. Moss agrees. "It's hard to believe that reducing hospitalizations by one or a few a year would make Orkambi cost-effective." Still, Moss says, there are also indirect factors to consider, such as the ability to work and the increased life span of those on therapy.

In April, the UK's National Institute for Health and Care Excellence (NICE) issued a proposal to assess the clinical and cost-effectiveness of Orkambi. But it's still early for any substantial cost-effective analyses or country budget impact from NICE or other institutions for Orkambi or even for Kalydeco. "Once NICE publishes its [analysis], we will have an idea of what evidence Vertex submitted in support of its health economic claim," says Leora Schiff, founder of Massachusetts-based Altius Strategy Consulting, who has assessed the cost burden of other expensive drugs for healthcare plans. "Companies have been launching drugs with claims of health economic benefits but no published data to back it up," she says. "Going forward, they're going to have to do a much better job of substantiating their claims."

Still, Kalydeco has had a relatively rapid reimbursement trajectory with both private payers in the US and with Medicaid, according to Vertex. Analysts expect a similar pattern with Orkambi. "The unmet need is generally just as high, there are no approved alternatives to address the underlying cause of disease, and the drug has shown statistically significant and clinically meaningful reductions in exacerbations and hospitalizations," says Yee. "These are the important aspects that payers can appreciate." In a recent analysis, Avalere Health, a healthcare advisory firm, and America's Health Insurance Plans, an advocacy group for the US health insurance industry, projected that by 2024, 40% of Orkambi's cost will be covered by Medicaid, about 53% by private payers, and the rest by either Medicare or the state-mediated exchanges.

Analysts are more concerned about reimbursement of Orkambi in Europe and other countries that negotiate on price. Access to Kalydeco in European companies was delayed, mostly owing to country-by-country price negotiations. In Australia, the drug was approved 12 months after FDA approval in July 2012 and was publically reimbursed only in October 2014. "Orkambi impacts three to five times more patients than Kalydeco's current label in the United States, so the budget impact will be larger," says Yee. "Unlike the US, these countries have fixed budgets carved out. There will be hard negotiations to agree on a price," he says. "Vertex will need to make a solid pharmaco-economic argument for those governments. It's that simple."

Although slow going, Nadeau says he expects even price-sensitive countries to come on board with reimbursement for Orkambi, just as with Kalydeco. "Ultimately, there are no similar therapies available, so I think reimbursement will come through around the world," he says.

Towards the holy grail

Despite the sticker shock, clinicians are looking towards newer, more efficacious treatments. The community is looking forward to this first triple combo of Orkambi plus a second corrector, says Moss. "A lot of us think that is where the future of cystic fibrosis treatment is. Like in HIV, you need a multiple-front attack to get really high effectiveness in the [greatest] number of patients."

Cocktail regimens that can treat a wider range of patients have already been developed for hepatitis C (HCV) and HIV. Certainly, Vertex's ultimate goal, says Negulescu, is a cocktail that targets the majority of the cystic fibrosis population with meaningful efficacy. "A cocktail developed by a single company will have a price advantage for patients and payers," says Yee. "A combination with drugs from different companies becomes very challenging because each one wants their share of the revenue. We saw this with HCV where the price of combinations was driven down when a single company developed the entire cocktail."

With HIV and HCV, it has not necessarily been the best-in-class molecules that go into the most widely used combinations. "The combinations that are safe, effective and most convenient to take are the ones that take the majority of the market," says Nadeau. "I think we will probably see the same paradigm develop for cystic fibrosis."

According to Preston W. Campbell, the new president of the Cystic Fibrosis Foundation, despite the high cost of Orkambi and Kalydeco, many patients have been able to gain access because most payers "understand these are transformative therapies for patients who have been waiting their entire lives for a treatment that goes beyond addressing solely the symptoms of cystic fibrosis," he says. "But our work doesn't stop until we have a cure for all people with cystic fibrosis. This is an extraordinarily exciting time for the cystic fibrosis community."

Anna Azvolinsky, New York

Table 1 Selected cystic fibrosis clinical programs in late clinical development

Drug name	Company	Current phase	Target
VX-661	Vertex Pharmaceuticals	Phase 3	CFTR corrector
Translarna (PTC124)	PTC Therapeutics	Phase 3	Exon-skipping molecule for CF patients with nonsense mutations
GL67A/pGM169	UK Cystic Fibrosis Gene Therapy Consortium	Phase 2b	Cationic liposome complexed with codon-optimized plasmid DNA for CFTR
P-1037	Vertex Pharmaceuticals	Phase 2	Sodium channels

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