The new classes of cancer immunotherapies hold great, exciting clinical promise across a number of cancer types, with the potential of extending the lives of patients who previously had no options. But these drugs also come with an eye-watering sticker price, with courses of treatment costing hundreds of thousands of dollars.
As more indications for already marketed drugs are approved and new drugs come out of the pipeline, payers across the world are grappling with how to evaluate these drugs and deciding whether they are worth the cost of making them available to patients. When the concept of value can vary from country to country, payer to payer, clinical group to clinical group, patient to patient, how can all these viewpoints of value be reconciled? The good news is that ISPOR members strongly believe that there will be a more unified evaluation of the value of cancer immunotherapies, and payers in the United States will catch up with health technology assessment (HTA) bodies around the world.

**EUROPEAN VS. US VIEWPOINT**

“Most of the United States has a different approach; particularly in the public sector, there are not really any assessments for economics or value,” says Michael Drummond, MCom, DPhil, University of York, and one of the Co-Editors in Chief of *Value in Health*. “CMS [Centers for Medicare & Medicaid Services] approves everything in cancer as soon as the FDA [Food and Drug Administration] licenses the drug.”

Meanwhile, in Europe, there are 3 general approaches to assessing the value of drugs. One is “kind of like the United States, which is next to nothing,” according to Drummond. These countries, predominantly in Southern Europe, do not conduct any assessments beyond what the licensing agency does to grant approval, an approach that he called “sparse.”

In central and northern Europe, there are 2 approaches. The more common approach is to assess the incremental costs based on quality-adjusted life year (QALY) and then make a formal or informal judgment about whether the drug gives enough in terms of improved length and quality of life in relation to the cost. The United Kingdom is the most formal in this approach, but the Scandinavian countries, the Netherlands, the Republic of Ireland—all of western and northern Europe—would follow this kind of assessment.

The other approach, particularly in Germany and France, involves assessing clinical value on a scale of 1 to 5. In France, a score of 1 is good and 5 is bad; Germany is the reverse. The clinical grading, Drummond says, assesses how much the drug adds to current therapy. So long as the assessment shows that there is some value, irrespective of how much it is judged to be, the drug is allowed to be paid for and there will be price negotiations. “In France it’s a little bit more closely defined than Germany, but in France if you get a score of 1 based on the clinical assessment, you can demand a price basically without any discount. But if you get a 4 or 5, you’re going to have to take a discount to get the drug on the market.”

In terms of the PD-1 immunotherapies, despite the rigor of the UK approach, the first 2 approved—Bristol-Myers Squibb’s Opdivo (nivolumab) and Merck & Co.’s Keytruda (pembrolizumab)—“have pretty much been recommended,” Drummond says. “In a couple of cases, depending on the indication, there’s been the requirement to give the government some kind of a price cut.”

The overall presumption in Europe is that these immunotherapies will work and provide long-term value. In the richer European countries, the drugs have gone through the value assessment and “come out the other side with mostly a positive determination,” according to Drummond. “Obviously in the long run, who knows whether these drugs really work, but I think the presumption is that they do.”

In the US private sector, while there are a couple of value assessment frameworks (such as those created by American Society of Clinical Oncology [ASCO] and Memorial Sloan Kettering), “in terms of considering value, it’s still pretty rudimentary at the moment,” Drummond says. The reasons for this are several, including commercial pressures and Medicare’s limited negotiating powers.

As the immunotherapy market expands with more drugs and indications for these approved drugs, Drummond expects there will be rebates in the US private sector and deals cut to offer lower prices to certain health plans. “Those rebates are generally confidential but everybody knows that they exist, and I expect that there will be a little bit of price competition.”

In both Europe and the United States, there is little pricing transparency for any drug. “In the United Kingdom, you can go on our website for the National Institute of Health and Care Excellence [NICE], and you can look up nivolumab, and it will say that it was recommended for use in an indication, and it might say ‘providing the conditions of the Market Access Agreement are met,’ or it might say something like ‘providing the commercial arrangements agreed with a company will apply.’ This essentially means some kind of to-and fro-ing on price, but all that there is disclosed is that there is an arrangement. In terms of the price cuts, it certainly doesn’t say what those price cuts are,” Drummond says. “We happen to know in the university because we do evaluations for NICE, we have to put the numbers in to calculate cost effectiveness, so we will know what the price cut is in a given situation but we are not allowed to reveal that.”

Discounts offered by the manufacturers, however, will make the price less than the international reference price. “That’s what we have to live with right now, but I think one day the international reference price comparison will be out the window, because nobody can believe any prices they see,” Drummond says.
There are also agreements in Europe, particularly the United Kingdom, in which the manufacturer will refund part of the price, get credit for a future drug, or make another concession if the drug is not shown to work.

In one of nivolumab’s indications, for treating locally advanced or metastatic nonsquamous non-small cell lung cancer in adults after chemotherapy, NICE will review how the drug is working after 2 years; if it not working, the patient will have to stop treatment—but refunds are not required. "In other deals, there is a fairly complicated arrangement for what outcomes should be obtained, and if they’re not obtained, there could be refunds," Drummond says. “But my understanding with the PD-1s, there haven’t been any of those more complex deals. We know if the drug is still working for the patient, the drug is going to deliver, so we can continue.”

Drummond says in the future, based on how more countries are looking more intensely at value, he expects US payers to also start looking. “The vacuum left by government is being filled by professional groups and by private plans.” In the case of ASCO, the group’s concern over value was not about overall cost but of cost to the patient, and patients should be informed because they will have to pick up part of the price of these drugs in copays.

ISPOR’s Initiative on US Value Assessment Frameworks task force is promoting the development and dissemination of high quality, unbiased value assessment frameworks.

The US market is also more complex because some payer groups, in terms of lives insured, are large enough to constitute a European country while others are quite small. “So it’s hard for those smaller plans to do the kinds of rigorous assessment that you expect from a payer like the United Kingdom,” Drummond says.

The rise of the Institute for Clinical and Economic Review (ICER) in the United States, which did a review of PD-1 inhibitors in lung cancer 18 months ago, has been a particularly interesting development. “It was clear that no one would be trusting the government in the United States to be doing something like that because the level of trust in government is quite low compared to government in the United States, which did a review of PD-1 inhibitors in lung cancer. “You could clearly see that the clinical impact, or maximum two-year budget impact, so they are more keen on show me the activity initially, and then tell me the story of long-term survival or some other point,” Dhawan says. “That’s the challenge we continue to face, how do you balance that when you have payers looking at value in different ways. But we do one thing that is fairly agreeable and that is we need to continue to collect this long-term data and show the long-term value from a survival standpoint.”

Dhawan believes that payer attitudes in the United States are changing, albeit slowly. Part of that is due to the rise of independent groups such as ICER. “There is that natural evolution that’s happening in the marketplace, people are starting to look at value from a different perspective, and from a more holistic perspective. ICER is not only looking at value from an outcomes standpoint, but also from a cost effectiveness standpoint. That is going to provide some more perspective about the value and help payers make those decisions.”

Although ICER has come under criticism by some manufacturers and patients about how it makes its evaluations, fearing lower payments from government and denial of treatment from insurers, Merck was actually “very pleased” with ICER’s evaluation of PD-1 inhibitors in lung cancer. “You could clearly see that the clinical evaluations, the clinical outcomes, the methodologies they used, the analyses they used were pretty sound,” Dhawan says. “They were actually in line with what, from Merck’s standpoint, we submitted in our submission package to them, and in line with our thinking. Of course, you have to look at the standpoint of a cost per life-year gain, we’re pretty much on line with where ICER was. It’s only when you start to look at some of the quality of life data and cost per QALY numbers that we started to have some methodological differences. But cost per life-year gained, if that is the measure that payers can use to determine value, that is something that the manufacturers and ICER and the payers can collectively look at and utilize.”

One thing is clear, Dhawan says—the ways that value is measured have to evolve. “Everyone is talking about how the evaluation of value cannot be just focused on the narrow ways of looking at the effectiveness and safety and patient-reported outcomes, it has to be more holistic,” he says. “And I think there’s a big conundrum.”

ISPOR’s Initiative on US Value Assessment Frameworks task force is promoting the development and dissemination of high quality, unbiased value assessment frameworks. The task force has released a draft white paper with recommendations such as building upon cost-effectiveness analysis; applying cost-effectiveness analysis to inform public and private coverage and reimbursement decision making; managing budget constraints and affordability; and encouraging users of alternative value assessment to gauge their usefulness in terms of consistency, reliability, and fairness in the broader context of healthcare decision making.
“The evolution is going to continue and people are going to form a methodological standpoint to bring different aspects and find ways to not only bring the patient-reported outcomes data along with safety or efficacy, but also a more softer way of looking at patient-centric data and symptom improvement. And also start to look at different perspectives—whether it’s a societal perspective, or a payer perspective, or it’s a physician perspective, or a patient perspective—different definitions of value,” Dhawan says. “I think we are headed in the right direction, as slowly, payers are bringing different points of view into the value calculation, and we’ll find a way to assimilate all of that.”

MEANWHILE, IN JAPAN
Japan’s Ministry of Health, Labor, and Welfare uses 3 factors to evaluate a drug for approval: safety, quality, and efficacy. Japan has had sophisticated HTA systems at both the micro and macro levels since 1961, when universal healthcare was first introduced in Asia. Approval, reimbursement, and pricing for new technology (drugs and devices) is all controlled and determined based on rules from Ministry of Health, Labour and Welfare (MHLW), according to Isao Kamae, MD, DhPh, professor of pharmacoeconomics in Japanese Pharmaceutical Manufacturer’s Association (JPMA) Project, Keio University, Japan. “The equations for official pricing have been developed in a subjective way, based on political considerations and historical precedent,” Kamae says.

Value definition and determination in Japan is a mixture of political and scientific approaches, with “Japanese-style value-based pricing,” Kamae says. Once the price is determined, the new technology is subject to be listed on the National Formulary for reimbursement unless the company withdraws. Re-pricing is done biennially and the discounting rate is determined by MHLW, with a constant reimbursement rate of 70% applied automatically for all technologies after first being listed. The manufacturer defines the position of a new drug in multi-outcomes according to the value of the drug, with the government asking developers to define “clinical” value. This value includes quality of life for patients, as well as implicitly defining the drug’s broader social benefit. Value for money was implicitly determined until March 2016, when an explicit measure such as cost/QALY was officially used. In April 2016, MHLW introduced a pilot appraisal of cost effectiveness for 7 existing drugs and 6 devices, in response to public concerns about high-cost drugs and devices. This program will be fully implemented and extended to new drugs and devices in 2019 or later, Kamae says.

When it comes to the new cancer immunotherapies, valuation and pricing depends on certain factors that actually apply to every drug approved. Keytruda was approved one year ago in Japan, and therefore has another year to go before its pricing is reconsidered under MHLW rules. But Opdivo (nivolumals), which was the first PD-1 to come to market in Japan in September 2014, has undergone repricing. In the case of Opdivo, a special discount rule was applied. This rule is invoked if a new drug attained a large amount of sales larger than expected at the approval. “We call it market extension re-pricing, which is one of the cost-control mechanisms in Japan,” Kamae says. “So considering the extreme budget impact by Opdivo (more than about $3 billion US per year), MHLW applied the Market Extension Re-pricing rule by having politically changed the method as an emergency response, and the price of Opdivo was discounted by 50%.”

“The evaluation whether or not MHLW can control costs by introducing cost-effectiveness requirements is still left for future investigation,” Kamae says.