SPECIAL SERIES: ECONOMIC ISSUES IN CANCER CARE

Precision Medicine in Oncology II: Economics of Targeted Agents and Immuno-Oncology Drugs

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INTRODUCTION

Medical oncology is experiencing a transformative shift away from traditional cytotoxic chemotherapies toward targeted small molecules and immune-oncology (TA/IO) drugs. Although biomarker-driven therapy has been successfully used in select cancers for decades, such as estrogen receptor–positive breast cancer, diagnostic and therapeutic advances have increased the application of precision medicine across an array of cancers. Of the 31 new molecules approved for cancer indications by the US Food and Drug Administration (FDA) between 2017 and 2018, 28 were TA/IO drugs.[1] However, a full realization of the clinical potential of these agents is hindered not only by mechanistic and biologic considerations, but also by the economic milieu of contemporary cancer research, health policy, and care delivery. In this article, we explore the economics of precision medicine in oncology, with a focus on TA/IO drugs. We first discuss the unique challenges of developing therapeutics in the era of precision oncology, before exploring payer, provider, and patient considerations. Last, we discuss the cancer research ecosystem, with a focus on TA/IO drug development and evaluation, affecting decision making by each of these stakeholders. By presenting distinct, albeit interconnected, perspectives, we hope to highlight the economic challenges and potential solutions to realizing the promise of TA/IOs in modern oncology.

DRUG DEVELOPMENT IN THE ERA OF PRECISION ONCOLOGY

Developing targeted agents poses unique challenges. These include identifying suitable molecular targets, designing a complementary agent, conducting research that demonstrates the safety and efficacy of targeted compounds, and then identifying a suitable and sizeable market for the new agents. Regarding molecular targeted therapies, these agents are rarely developed in isolation, because companion diagnostics must also be developed and validated.[2] This adds initial costs and uncertainty to developing precision therapies, given that the success of the therapeutic agent relies in part on selection of the correct biomarkers, the right tests to identify them, and in some cases, optimal cutoffs to define the target population.[3,4] As a result, the FDA approval process has become more complex, because it involves navigating regulatory pathways for both therapeutics and companion diagnostics. However, once a validated molecular target and companion diagnostic are identified, subsequent development of follow-up drugs can be rapid.[5]

Market size represents another important consideration, because an inherent benefit of precision therapy is the targeting of subpopulations that are most likely to benefit. This limits the number of patients who are eligible to receive a novel therapy. For instance, in a cohort of patients with non–small-cell lung cancer (NSCLC) undergoing broad-based genomic sequencing in real-world practice, approximately 15% had a epidermal growth factor receptor tyrosine kinase mutation, 4% had an anaplastic lymphoma kinase mutation, and the prevalence of many other genetic alterations (ie, MTOR, KIT) hovers at approximately1%-2%.[6] Hence, with approximately 80,000 people diagnosed in the United States with advanced NSCLC each year, fewer than 17,000 will have a targetable genetic alteration for which there is currently an FDA-approved drug.

The rarity of many driver mutations has also altered the economics of clinical trials, because new trial designs are required to efficiently identify and recruit research participants. For instance, when uncommon genetic alterations are present across multiple tumor types, “basket” trials can allow for tissue-agnostic study enrollment.[7] Conversely, “umbrella” trials incorporate tumor profiling of patients before assignment to one of many treatment arms. In the case of the Lung-MAP study (ClinicalTrials.gov identifier: NCT03851445), 10,000 patients with NSCLC will be screened for over 200 mutations before matching to investigational therapies.[8] Because a particular industry sponsor may only be interested in one of these mutations, trial designs such as this have fostered multistakeholder collaboration. As a large public-private partnership, the Lung-MAP study is supported by the National Cancer Institute and includes 8 different pharmaceutical partners and lung cancer advocacy groups, which increases recruitment efficiency but adds complexity to the research process.[9]

Another challenge to evaluating the effectiveness of new agents is that the standard of cancer care is

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evolving continuously. There have been 53 new cancer therapies approved by the FDA in the past 5 years. This poses substantial challenges to study design and data interpretation: comparison treatments that were selected to establish efficacy at the time a study is initiated may no longer be standard of care by the time the study is completed. Hence, it is difficult to evaluate the incremental benefit of new therapies, compared with contemporary standards of care.

To summarize, the development and marketing of TA/IO therapies pose unique challenges to the industry that have required new approaches to trial design, regulatory guidance, and support. Cancer research is expensive and complex. The actual costs of bringing a new drug to market are unclear and a subject of debate, with estimates varying from $658 million to nearly 4-fold higher.[10,11] Either way, these research costs are quite high, yet record investment into new TA/IOs continues. Between 2013 and 2015, the number of immuno-oncology alliances between big pharma/biotech and small enterprises grew from 6 to 58. As of 2017, there were 248 new I/Os under development. Moreover, the financial rewards are outweighing the inherent risks of research: the price of new cancer therapies has increased 10-fold over the past 20 years, and the median price of a new cancer TA/IO drug is more than $150,000 per year.[12,13] And these high prices, even in the face of a risky and expensive risky research endeavor, contribute to substantial profits. In 2013, the profit margin for pharmaceutical companies ranged anywhere from 10% to 42%, with an average of 18%.

PAYER AND PROVIDER PERSPECTIVE

The exponential increase in cancer drug prices has had a transformational impact on the cost of cancer care: US cancer drug spending doubled between 2012 and 2017, and is expected to reach $200 billion worldwide by 2022. These increasing expenditures have raised concerns about the sustainability of health care financing systems in the United States and abroad. However, approaches to reducing prices of new cancer therapies, for which TA/IOs make up the majority, and addressing affordability differ greatly between the United States and other high-income nations.

High-Income Nations (ex-US): Drug Approvals and Coverage

Regulatory pathways for TA/IO drugs and companion diagnostics share considerable similarities across high-income nations. For example, all cancer drugs licensed in Europe require centralized review from the European Medicines Agency (EMA). Much like the FDA in the United States, EMA marketing approvals are based solely on the safety and efficacy of investigational compounds, with prices and comparative effectiveness not factoring into their licensing decisions. Furthermore, the EMA has recently adopted strategies mirroring the FDA to more formally evaluate companion diagnostics and speed up the approval of drugs targeting critical unmet medical needs.

Although parallels exist across regulatory authorities in the United States and other high-income nations, the post-licensing period stands in stark contrast. In most other high-income nations, regulatory approval for marketing does not guarantee either coverage by payers or immediate universal access to newly approved agents. Rather, most nations use health technology assessment (HTA) bodies or reference pricing to inform the coverage decisions and reimbursement policies once a therapy gains marketing approval. Importantly, these reviews and subsequent reimbursement negotiations accept that not all drugs deemed safe and efficacious by regulatory bodies add enough value to be made widely available to patients. For example, blinatumomab, a bispecific CD19-CD3 T-cell engager, received EMA marketing approval for acute lymphoblastic leukemia in November 2015, but remains without coverage approval in 8 of 12 evaluated European nations.[14]

The era of precision oncology has brought 3 main challenges to conducting robust HTA reviews and well-informed reimbursement negotiations. First, an increasing number of TA/IO drugs receive marketing approval on the basis of single-arm, uncontrolled studies,[15] creating uncertainty as to the appropriate comparator when conducting comparative-effectiveness analyses. Second, the growth in approved cancer therapies and expanding treatment indications has challenged the ability to efficiently conduct HTA reviews and offer timely coverage guidance. For example, the time between marketing approval and subsequent coverage decision averaged over 600 days for recent cancer medications in Australia[16] and 405 days in England.[17] Last, the use of companion diagnostics alongside novel cancer therapies has increased the complexity of HTA and reimbursement decisions, with cost-effectiveness of many TA/IOs now influenced by both the expense of the diagnostic test and proportion of patients tested eligible for the treatment.

US Drug Approval = US Payer Reimbursement

Pricing and reimbursement of cancer therapy is considerably different in the United States. Both insurance regulations and market fragmentation currently limit the viability of HTA to inform cancer drug formularies in the United States. Laws in at least 36 states mandate that commercial insurers cover all FDA-approved cancer therapies, and large federal payers (ie, Medicare and Medicaid) have similar provisions. Requiring that every FDA-approved anticancer drug must be reimbursed limits the effectiveness of drug price negotiations. Furthermore, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 explicitly restricts Medicare from directly negotiating with manufacturers. It should come as no surprise that TA/IO drugs in the United States have higher prices than

other high-income nations. Although transparency around drug pricing and rebates are lacking, an analysis from the US Department of Health and Human Services estimated that US office-administered cancer therapies cost an average of 1.8 times more than other high-income nations.[18]

High drug prices have influenced how cancer care is delivered in the United States. Here, office-administered therapies, including I/Os and many oncolytics, are purchased by the physician or practice and billed to patients and/or insurers after administration. The margins from this "buy and bill" system contribute to more than 50% of all revenue generated by US-based medical oncologists.[19] Reimbursement of office-based infusions is more generous when administered in the hospital setting, including community-based offices owned by a hospital.[20] Unsurprisingly, there has been a dramatic increase in "vertical integration" between physician-owned offices and hospitals. Furthermore, as the number of orally administered TAs has increased, so too has the growth of practice- or hospital-owned specialty retail pharmacies that dispense these oral oncolytics.[21]

In aggregate, the high costs of TA/IOs may provide a strong incentive for physicians to adopt them: available research suggests cancer therapy selection may be associated with financial incentives,[22-24] and most present-day market dynamics in the United States incentivize incorporation of high-cost novel therapies. Combining this with a favorable regulatory environment and policies that require near-immediate insurance coverage of all FDA-approved cancer therapies, it should come as no surprise that adoption of novel TA/IOs in the United States is swift. In the setting of I/O drugs, this translated into US patients receiving checkpoint inhibitors up to 2 years before they were reimbursed in other high-income nations (Fig 1).[25]

High treatment costs have a profound impact on patient access to, and financial toxicity from, TA/IOs. Health

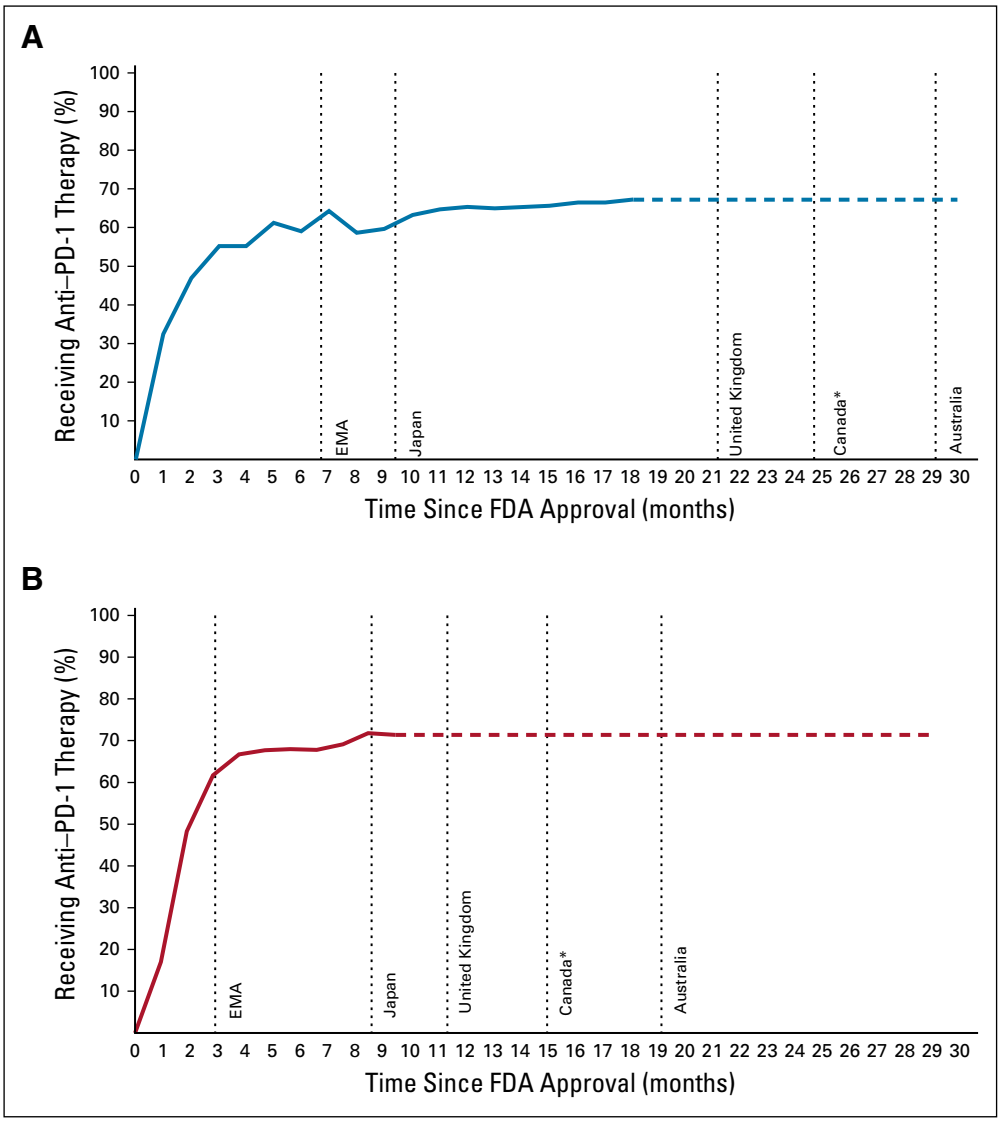

FIG 1. Marketing approval and adoption of anti–programmed death-1 (PD-1) therapy in the US compared with other high-Income nations. (A) Advanced non–small cell lung cancer. (B) Advanced renal call carcinoma. Percentage receiving PD-1 in the United States derived from O'Connor et al[25]; dashed horizontal trend lines represent predicted anti–PD-1 use. Vertical dashed lines represent ex-US approvals and/or reimbursement of anti–PD-1 therapies. FDA, Food and Drug Administration; EMA, European Medicines Agency. (*) Reimbursement in the province of Ontario, Canada.

insurance rates have increased substantially over the past decade, and insurance is meant to protect beneficiaries from catastrophic medical expenses. As noted, there are broad requirements for both commercial and federal insurers to cover virtually all TA/IOs for approved indications and off label for compendium-listed indications.[26] However, reimbursement levels relative to payer-negotiated drug prices can vary substantially and place patients at risk for significant out-of-pocket expenses. Patients may pursue a variety of strategies to limit out-of-pocket exposure, but in many cases, they experience significant financial burden, with downstream implications.

Insurance Coverage Mechanisms for TA/IOs and Implications for Cost Sharing

TA/IOs may be either parenteral or oral. In the United States, insurers tend to cover them through the medical and prescription drug benefit mechanisms, respectively, with different implications for out-of-pocket costs to patients. Regarding parenteral therapies, the traditional Medicare fee-for-service (medical) benefit, which covers two thirds of beneficiaries, applies a coinsurance rate (a percentage) to the full cost of a "visit," with patients liable for a deductible and then 20% of total approved reimbursement amount. Because Medicare lacks an out-of-pocket cap, the patient liability is open ended and may be quite substantial. However, 80% of Medicare beneficiaries with the traditional benefit supplement Medicare coverage with a retiree plan from a former employer, a Medigap plan, or Medicaid, and these supplements generally cover a major portion of the patient liability after Medicare reimbursement. One third of Medicare beneficiaries are enrolled in Medicare Advantage (health maintenance organization or preferred provider organization) plans that may also use a 20% coinsurance rate for parenteral chemotherapy, but include a $6,700 cap on total out-of-pocket spending, not present under the fee-for-service benefit.[27]

Patients enrolled in commercial and self-insured employer plans may also face substantial out-of-pocket costs. For example, a study using administrative claims estimated a per-patient monthly out-of-pocket cost for parenteral TAs of $908 in 2011 (nearly $11,000 annually).[28] Since the period reflected in that study, out-of-pocket caps were mandated by the Affordable Care Act. The benefit of the out-of-pocket cap may be countered by the increasing enrollment in high-deductible health plans, which concentrate the out-of-pocket requirements up front and may create a barrier to treatment initiation. High-deductible plans have been shown to be associated with less timely cancer treatment[29] and higher out-of-pocket spending for cancer treatment,[30] although there is available evidence specific to use of TA/IOs.

A large and growing proportion of TA/IOs are orally administered agents, and most insurers cover these under a pharmacy benefit. Here, cost sharing may vary dramatically depending on formulary inclusion and tier placement. Unlike parenteral TA/IOs, for which the patient is billed weeks after administration, the patient encounters the out-of-pocket cost at the point of purchase, potentially generating sticker shock and forcing immediate decisions regarding whether to purchase the drug.[31] Several single-institution studies have reported high rates of patients seeking charity care or help from patient-assistance foundations associated with treatment with TAs,[32-34] but there is limited population-based data concerning prevalence and level of support, because their contribution may not be recorded reliably on prescription drug claims. Patients who are unable to meet high out-of-pocket costs may fail to obtain their prescriptions,[35-37] discontinue the medication early, or engage in various forms of cost-related nonadherence, including skipping doses, splitting pills, or delaying refills. Patients faced with open-ended financial outlays for newer TI/AOs may choose to receive older cytotoxic therapy covered through Medicare Part B and their supplemental insurance.

Although issues of tier placement and out-of-pocket price are relevant to almost all prescription benefits, there has been a focus on targeted therapy use within the Medicare Part D benefit. The standard Part D benefit includes dramatic shifts in beneficiary cost sharing over the benefit year, initially including a coverage gap and a catastrophic phase, during which the beneficiary pays 5% of the total negotiated price of the drug. For high-priced oral TAs, beneficiaries might reach the coverage gap or even the catastrophic phase with their first prescription fill.[38] As a result of the Affordable Care Act, the coverage gap began to close beginning in 2011. Despite this coverage change, the increase in drug prices over time has likely wiped out most potential savings; among 13 oral TA/IOs, mean 12-month out-of-pocket liability grew from $8,794 in 2010 and is expected to be $10,470 by 2019. We note that these estimates may overstate the actual out-of-pocket expense to the extent that patients receive support through patient-assistance foundations. Dual-Medicaid-enrolled and other low-income beneficiaries qualify for "extra help" or the low-income-subsidy (LIS), which dramatically reduces out-of-pocket prices. LIS receipt was associated with increased probability of initiating targeted therapies[37,39,40] and shorter time to initiation among those who initiated.[36,37,40] Evidence on adherence[39,40] and duration[39] related to LIS receipt is mixed.[41]

Downstream Economic Effects of TA/IOs

There are downstream direct and indirect costs associated with cancer treatment, including costs associated with management of treatment of adverse reactions as well as indirect costs, including travel and time costs for the patient and caregivers. Although empirical work is currently limited, TA/IOs have the potential to be associated with fewer and less severe complications compared with traditional

cytotoxic drugs, resulting in a reduction in emergency department visits and inpatient admissions for management of acute toxicities. Oral TA/IOs, in particular, may require fewer physician office visits, with reduced direct costs and lower indirect travel and time costs.[42] Furthermore, receipt of oral targeted therapy compared with parenteral treatment was shown to reduce the impact on the labor force in adults with multiple myeloma or lung cancer.[42,43]

Financial Toxicity

The exorbitant costs associated with cancer treatment, particularly the newer TA/IOs, may result in financial toxicity. Financial toxicity is the financial hardship that may be associated with patient and family spending on cancer treatment, surveillance, and long-term survivorship, similar to other adverse effects of therapy. As previously noted, anticipated financial hardship may result in failure to initiate treatment in a timely manner or reduce treatment adherence or duration, with concomitant reductions in clinical benefit. There are additional objective and subjective effects of financial toxicity, including poorer quality of life; poorer physical, functional and emotional well-being, anxiety, and depression; and increased mortality.[28,44-54]

IMPLICATIONS OF THE TA/IO CANCER RESEARCH ECOSYSTEM

The current cancer research ecosystem represents a driver of discovery, yet also a critical barrier to the optimal impact of TA/IO drugs at the population level. Progress in precision oncology has been largely fueled by industry investment. In the United States, biomedical research expenditures have almost doubled, from $59.5 billion in 1994 to $116.5 billion in 2012 (in constant 2012 dollars), with industry accounting for 46% of these funds in 1992, 59% in 2012, and 67% in 2017. Conversely, over the past decade, the National Cancer Institute budgetary purchasing power, grant funding rate, and research output (as measured by presentations at the ASCO annual meeting) have decreased.[55-57]

This shifting research funding landscape has important implications for decision making by patients, clinicians, payers, and policymakers. Pharmaceutical companies have a fiduciary obligation to their shareholders to focus their substantive research expenditures on developing new therapies, assessing their safety and efficacy in a manner consistent with FDA regulations, and bringing them to market as quickly as possible. Because these goals may not be entirely aligned with patient and societal interests, clear gaps exist in the current body of evidence supporting TA/IO therapies.

First, the corpus of research that is required to achieve regulatory approval may not be sufficient to guide clinical decision making. Patients enrolled in pivotal trials of TA/IO agents may not be reflective of the broader population.[25,58] For instance, patients enrolled in pivotal trials of pembrolizumab and nivolumab were only one third as likely to be older than 75 years of age, as were patients with the same cancer types in real-world practice.[25] FDA thresholds for marketing approval are also evolving, because the majority of TA/IO drugs are approved via the accelerated approval pathways, which tend to rely on surrogate outcome measures and are more likely to incorporate single-arm studies than traditional FDA approval pathways.[59-62] Furthermore, a key element of the accelerated approval pathway is the requirement for postmarketing studies. However, not all postmarketing studies are completed in a timely manner, leaving important knowledge gaps.

Second, as the knowledge base regarding TA/IO drugs increasingly relies on industry funding, critical clinical questions may go unaddressed. Many of these unanswered questions are ones in which government and payers should have a great interest, that is, how can we limit overuse, identify treatment strategies that offer the greatest value, and implement innovative cancer care delivery to improve clinical outcomes. The high costs of TA/IO drugs make research addressing important clinical questions expensive if a pharmaceutical company is not supplying the therapy. Furthermore, industry is less likely to support head-to-head comparisons, which may be essential for clinicians and payers. And even when the pharmaceutical industry and independent investigators address the same questions, industry-sponsored studies are more likely to yield results that are favorable to industry in clinical trials as well as cost-effectiveness studies.[63-66]

ADDRESSING AFFORDABILITY, IMPROVING ACCESS, AND REWARDING INNOVATION

Renewed investment outside of industry is needed to ensure HTA bodies, clinicians, and patients have access to meaningful comparative data in the era of precision oncology. Greater public funding of clinical trials through traditional grant mechanisms would be welcomed, but future partnerships with payers could also support important trial efforts. Looking back at a critical lesson in medical oncology where high-dose chemotherapy with stem-cell rescue was adopted into routine practice for breast cancer without robust comparative data, the definitive randomized trial that established this intensive approach did not improve clinical outcomes compared to standard chemotherapy was funded by a large US commercial health payer.[67] The Centers for Medicare & Medicaid Services (CMS) now recognizes that therapies and diagnostics are receiving marketing approval without robust comparative evidence. In many cases, CMS grants full reimbursement while additional evidence is obtained (ie, Coverage with Evidence Development), including broad-based tumor genetic sequencing. Combined with the historically permissive off-label reimbursement of FDA-approved cancer drugs in the United States,[68,69] one

expects some patients with cancer in the United States are now receiving targeted agents during routine practice on the basis of limited clinical data. In such areas lacking solid clinical evidence, CMS should consider limiting reimbursement and support robust clinical trials to ensure new treatments and diagnostics improve clinical outcomes compared with current standards of care.

Along with renewed efforts to ensure the most clinically relevant questions are addressed and actionable comparative data are produced, new approaches to drug regulation are needed. Therapies developed for precision oncology frequently target relatively small subgroups of patients, and the Orphan Drug Act (ODA) has played an important role in the development of TA/IO therapies. The ODA was established in 1983 to offer incentives to manufacturers using market exclusivity and tax credits to increase development of drugs for rare diseases. The ODA was written in an era when drugs developed for rare conditions would generate small sales and would not be profitable for manufacturers. However, the rise in drug prices now allows considerable revenue generation despite limited patient populations, with orphan drug designation adding significant value to public pharmaceutical companies.[70] The program should be updated to recognize recent profitability of orphan drugs and ensure future incentives minimize unintended consequences and reward therapies that address critical public health needs.

Even if future regulatory policies incentivize the development of valuable therapeutics and produce clinical data to support high-quality precision oncology, the affordability of TA/IOs must be separately addressed. A necessary first step in the United States will be to allow payers to restrict coverage of some approved, albeit low value, cancer therapies and create formularies with high-quality cancer drugs. Given that leading oncology professional organizations currently resist even the implementation of less restrictive step-therapy approaches, greater acceptance of necessary tradeoffs are needed before US payers are likely to be allowed to restrict reimbursement of approved cancer therapies.

Allowing US payers to restrict coverage of some TA/IOs with low value would enable more meaningful price negotiations like ex-US payers. However, regulatory approvals without strong comparative data are likely to continue, and HTA evaluations and formulary negotiations may remain challenging. Thus, additional coverage models may be necessary. Reference pricing and pay-for-performance are 2 such reimbursement strategies that could limit prices during evidence development and ensure TA/IO drugs are only rewarded if they improve important clinical outcomes compared with alternative treatments. Germany uses a different reimbursement approach to balance access with price controls. Here, manufacturers initially set the price of a new drug for a period of 12 months of market entry, affording time to conduct an HTA review and negotiate a price for month 13 onward.

SUMMARY

Unlike the formidable biologic barriers to fully realizing the clinical benefits of precision oncology, economic challenges are within our collective ability to address through renewed investment in clinical trials that produce actionable data and innovative health care policy and regulatory science. However, many stakeholders are faring quite well under the current system of developing and delivering TA/IO drugs—including the pharmaceutical industry, pharmacy benefit managers, commercial US payers, and many US providers and hospital systems—leading to considerable resistance to making necessary policy changes. Unfortunately, the stakeholders at greatest financial risk—patients and families—have the least influence to enact change. Time is of the essence to develop the evidence base to inform health policy and regulatory science that fosters a system where patients with cancer have affordable and equitable access to innovative therapies in the era of precision oncology.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Precision Medicine in Oncology II: Economics of Targeted Agents and Immuno-Oncology Drugs

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