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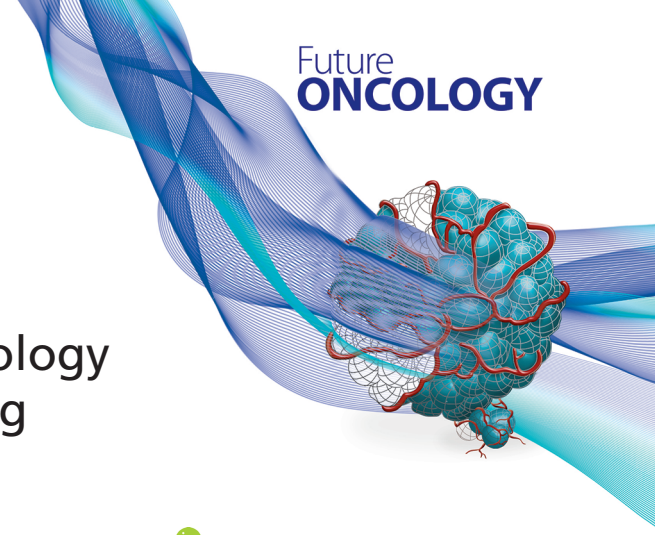

Use of real-world evidence for oncology clinical decision making in emerging economies

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Real-world evidence (RWE) can provide insights into patient profiles, disease detection, treatment choice, dosing strategies, treatment sequencing, adverse event management and financial toxicity associated with oncology treatment. However, the full potential of RWE is untapped in emerging economies due to structural and behavioral factors. Structural barriers include lack of regulatory engagement, real-world data availability, quality and integrity. Behavioral barriers include entrenched healthcare professional behaviors that impede rapid RWE understanding and adoption. These barriers can be addressed with close collaboration of healthcare stakeholders; of whom, regulators need to be at the forefront given their ability to facilitate use of RWE in healthcare policy and legislation.

Lay abstract: Traditionally, randomized clinical trials have been used to provide insights on new medical therapies and continue to remain the gold standard for approval. The-increasing availability of patient level data in the real-world, it is now possible to generate evidence regarding the usage and potential benefits or risks of a medical therapy derived from analysis of real-world data. This evidence is collectively referred to real-world evidence (RWE). randomized clinical trials and RWE are complementary and the area of Oncology especially benefits from RWE to guide clinical decision making across the patient journey. Key benefits include cancer screening and diagnosis, optimal treatment choices (including personalized medicine) and disease management such as dosing and treatment of side effects. In recent times, RWE generation in oncology has been prolific in the USA and western Europe. With expansive biopharmaceutical investments into infrastructure harnessing patient-level data and greater local regulatory guidance, oncology patients in emerging economies may now also have the opportunity to benefit from clinical decision making informed by RWE.

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Keywords: Asia-Pacific • effectiveness • electronic database • health policy • Latin America • Middle East • randomized clinical trials • real-world data • real-world evidence • safety

Randomized control trials (RCTs) are traditionally recognized as the gold standard for generating clinical evidence on treatment efficacy and safety. RCTs offer high internal validity through highly structured trial designs [1]. However, RCTs are resource-intensive, time-consuming, and have stringent inclusion and exclusion criteria that limit the generalizability of study results to the real-world [1,2,3]. Real-world evidence (RWE) can be used to complement RCTs as it can support the generation of insights on usage, benefits, and risks of treatment that have been collected from patient populations in clinical practice (e.g., electronic medical records [EMR], claim databases, registries and patient surveys) [4,5]. This use of RWE provides insights with fewer resources, lower costs, and a shorter amount of

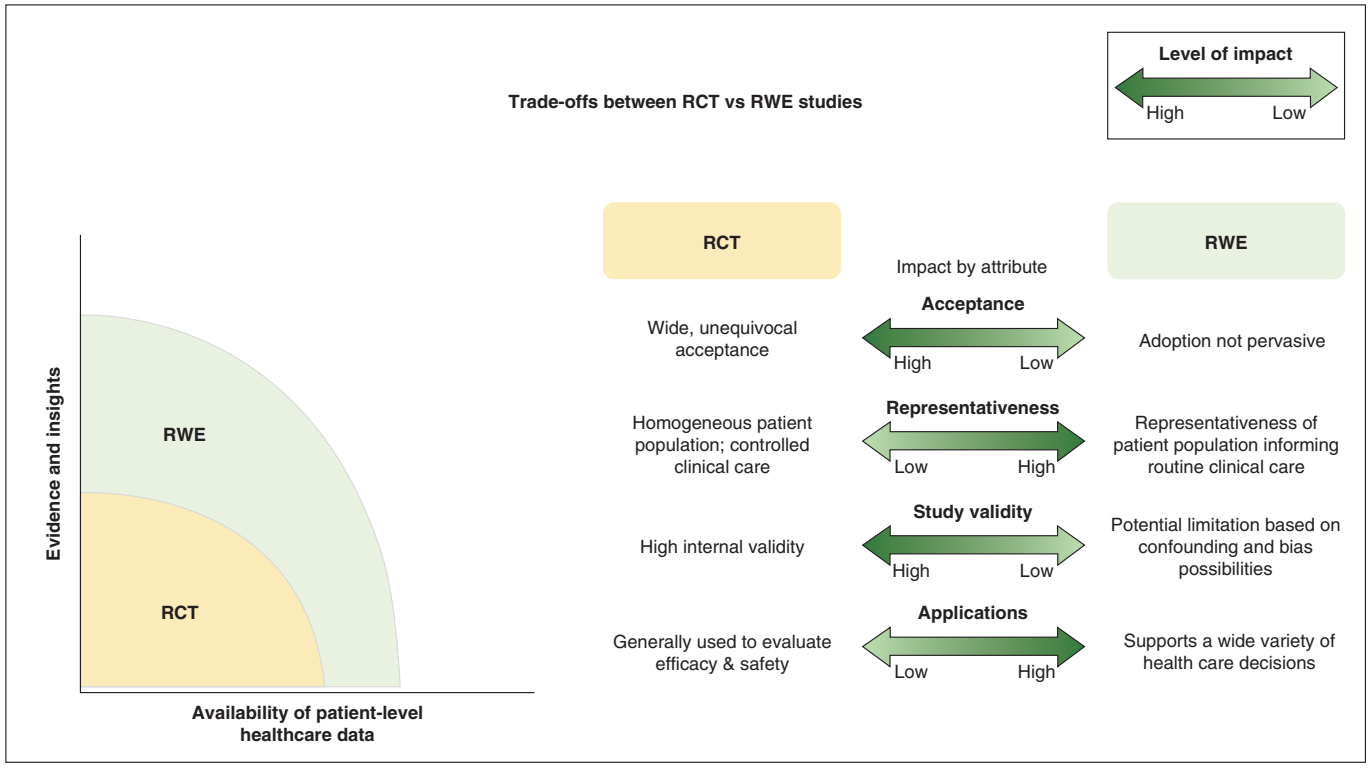

Figure 1. Tradeoffs between real-world evidence and randomized control trial studies.

time than traditional RCTs [6]. As detailed in Figure 1, tradeoffs exist between RWE and evidence from RCTs. These include limited stakeholder acceptance, questions around reliability and limitation of bias and confounders when generating RWE. Despite these tradeoffs, RWE complement RCTs by providing insights that have a high degree of external validity and can improve clinical decision-making for various therapeutic areas including oncology. For example, real-world overall survival is a measure accepted by oncologists due to it objectivity and comparability to overall survival (OS) data observed in RCTs [7,8]. Furthermore, the American Society of Clinical Oncology (ASCO) has provided guidance on classification around level of evidence, with RWE classified as level III or IV evidence, in other words, moderate to low strength. However, the ASCO guidance framework considers RWE as a valuable tool for clinical oncology research when it comes to answering questions not explored or considered feasible in RCTs [9].

RWE is anticipated to benefit stakeholders involved throughout the oncology care continuum, including healthcare professionals (HCPs), regulators, patient advocates and payers [10]. In particular, RWE has been used by oncologists to improve different aspects of clinical decision-making, such as patient profiling [11], disease detection [12], optimal dosing [13], understanding of treatment patterns [14,15,16] and management of adverse events (AEs) with greater confidence [17,18,19,20]. Additionally, RWE can inform treatment choices in light of financial toxicity; an important consideration for both patients and caregivers in emerging economies [21,22].

Regulators in the USA and the EU have supported the utilization of RWE by releasing guidance for RWE submissions and have shown a willingness to accept RWE for submissions related to drug approval and label expansion [4,23,24]. While USA and EU are viewed at the forefront of leveraging RWE, emerging economies are also witnessing a surge of interest in RWE. Among emerging economies, countries in the Asia-Pacific (APAC) region are leading the way in terms of RWE generation and adoption in comparison to the Africa and Middle East (AFME) region and Latin America (LATAM) region. This is evident from the trend in the number of real-world oncology studies published in these economies over the past 5 years (Figure 2) and acknowledgment of RWE by regulators in the emerging economies (Table 1).

Despite the upward trend of RWE studies (Figure 2), the full potential of RWE in clinical decision-making remains untapped due to barriers such as limited availability of quality real-world data (RWD), data integrity, entrenched stakeholder behaviors and lack of RWE expertise in interpreting and conducting RWE studies [25,26].

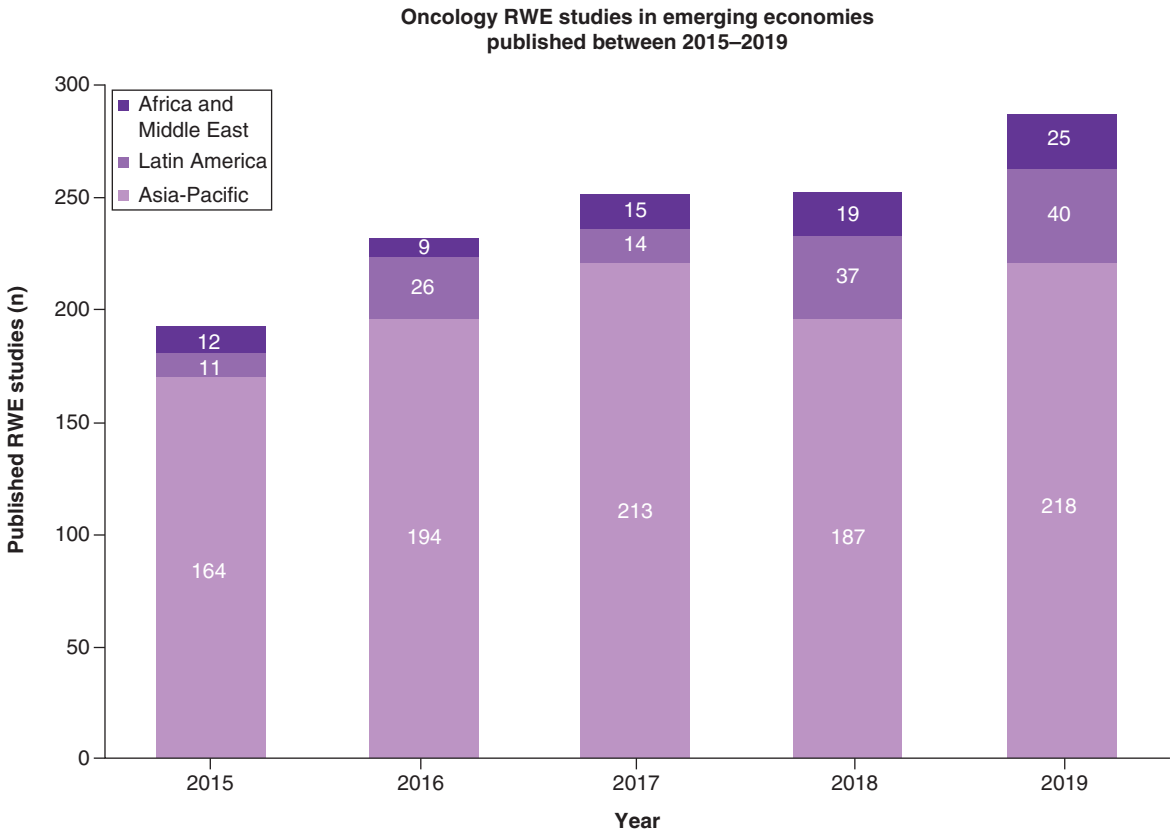

Figure 2. Oncology real-world evidence studies in emerging economies published between 2015 and 2019†.
†The regions considered for the search were APAC (China, Taiwan, Malaysia, Thailand, Philippines, Indonesia, India), LATAM (Argentina, Brazil, Colombia, Mexico, Chile, Peru), AFME (Algeria, Egypt, Jordan, Kuwait, Lebanon, Morocco, Nigeria, Qatar, Saudi Arabia, South Africa, Tunisia, UAE). Compound annual growth rate defined as the average year-on-year growth rate of RWE studies published over the past 5 years.
AFME: Africa and Middle East; APAC: Asia-pacific; LATAM: Latin Americ; RWE: Real-world evidence.
Source: PubMed.

Table 1. Definition of real-world data and real-world evidence by various regulatory agencies.

Regulatory Agency	Definition	Ref.
US FDA	RWD: any data on health interventions in routine clinical practice, and can be reported by providers, payers or patients	[4]
	RWE: the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD	
EMA	RWD: routinely collected data relating to a patient's health status or the delivery of healthcare from a variety of sources other than traditional clinical trials	[25]
	RWE: defined as the information derived from analysis of RWD	
China NMPA	RWD: all kinds of data related to patients' health status and/or diagnosis and treatment and healthcare collected on a routine basis	[26]
	RWE: clinical evidence about the use and potential benefits or risks of medical products, obtained through the analysis of RWD, including evidence obtained through interventional studies including retrospective or prospective observational studies or pragmatic clinical trials	
Taiwan FDA	RWD: data that is routinely collected and details the health status of patients or healthcare processes healthcare	[27]
	RWE: clinical evidence generated by appropriate analysis methods using real-world data as the source of information. This evidence can be used to help explain the use of drugs and their benefits and risks	
Saudi FDA	RWD: data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources	[28]
	RWE: clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD	

NMPA: National Medical Products Administration; RWD: Real-world data; RWE: Real-world evidence; SFDA: Saudi Food and Drug Authority; TFDA: Taiwan Food and Drug Administration.

Pragmatic solutions, including the development of regulatory RWE guidance, are needed to address each barrier to further increase the adoption and use of RWE in the emerging economies. This can be achieved through close collaboration between regulatory agencies, pharmaceutical companies and academic institutions [25,26].

This paper's objective is to identify benefits and major barriers associated with use of RWE for oncology clinical decision-making in emerging economies and propose pragmatic ways to address these underlying barriers. Recommendations are based on oncology expert opinions and desk research that include examples from RWE studies conducted in emerging economies.

Materials & methods

For the purposes of this paper, 'emerging economies' were defined as economies with low-to-middle per-capita income that are rapidly transforming into developed nations [27,28]. The emerging economies targeted in this review include countries from APAC (China, Taiwan, Malaysia, Thailand, Philippines, Indonesia, India), Latin America (LATAM; Argentina, Brazil, Colombia, Mexico, Chile, Peru) and Africa and the Middle East (AFME; Algeria, Egypt, Kuwait, Jordan, Lebanon, Morocco, Nigeria, Saudi Arabia, South Africa, Tunisia, UAE, Qatar).

A targeted literature review was conducted using PubMed to collect RWE oncology studies published between January 2015 to June 2020. In total, 1184 publications were identified which is presented in Figure 2. The search terms used include: 'RWE', 'RWD', 'real-world', 'routine clinical care', 'observational studies', 'case-controlled studies', 'cohort studies', 'cross sectional studies', 'external comparators', 'pragmatic trials', 'chart abstraction', 'EMR', 'health records', 'claims', 'registry', 'oncology', 'cancer', 'hematology' and 'tumor' (search string examples available in Supplementary Material 1). Targeted gray literature and government and relevant public agency websites were also reviewed. The literature review was used to better understand current applications and challenges associated with RWE use in emerging economies. The results of the literature review are presented in the subsequent sections of this review.

To supplement the literature review, we conducted interviews with five oncologists from APAC, LATAM and AFME, of which three oncologists are key opinion leaders (KOLs) in their field. The oncologists were approached via email and invited to participate in the interviews. Prior to obtaining consent for their participation, the oncologists were provided with context of the interview, including the rationale for conducting the interview.

The open-ended discussion questions that were used during the interviews are presented in the (supplementary Material 2). Topical areas included the impact of RWE on day-to-day treatment decision, regulatory landscape of RWE, applications and perception of RWE. The interviewers had no previous relationship with the KOLs/oncologists. In addition to providing the regional specific insights, two of the experts were also involved in the detailed conceptualization, development and oversight of this review.

Results & discussion

Traditionally, oncologists in emerging economies have relied on guidelines, such as the ASCO resource stratified guidelines and European Society for Medical Oncology Asia-Pacific, for oncology clinical decision-making [29,30]. However, there is a growing awareness on the benefits of RWE in understanding patient profiles, facilitating earlier disease detection and diagnosis, guiding treatment selection, understanding treatment patterns, aiding in AE management and informing treatment choices in light of financial toxicity. These benefits can enable oncologists to make optimal clinical decisions for their patients.

Patient profile

RWE can contextualize local patient profiles and dispositions to outcomes by factoring in demographic characteristics and patient behaviors. For example, the Haemato-Oncology Latin America (HOLA) study characterized multiple myeloma patients in Latin America and revealed hypertension, diabetes and heart disease as the most common patient comorbidities [16]. Elderly patients (≥65 years) had a greater comorbidity burden and were substantially less likely to receive autologous stem cell transplantation compared with patients aged <65 years. The study revealed age to be one of the key factors associated with treatment decisions in the region. Elderly patients were less likely to receive bortezomib-based therapy and more likely to receive chemotherapy compared with patients with age of <65 years. In addition, the study provided insights on treatment patterns in the region, such as demonstrating that bortezomib-based therapy was more frequently used in patients who were treated in private clinics and in patients who underwent autologous stem cell transplantation [16].

Disease detection

Early detection and diagnosis of cancer is the cornerstone to successful oncology treatment, with RWE having the potential to play a critical role, such as through appropriate screening programs. For example, Ma *et al.* conducted an RWE study in rural China, aiming to understand the effectiveness of cervical cancer screening programs by comparing three available cervical cancer screening methods. This study factored cervical cancer detection performance and real-world clinical considerations, such as training requirements and specimen collection. Based on these considerations, this study concluded that the human papillomavirus test was the preferred diagnostic test in low-resource regions [12].

Treatment choice

As mentioned earlier, patient profiles differ across geographies, including demographics, genetic characteristics and patient behaviors, all of which have an impact on treatment response. HCPs can use RWE as a lever for selection of appropriate treatments based on a better understanding of patients' needs. The OSSMAR study revealed that sunitinib is an effective and safe treatment for metastatic renal cell carcinoma patients in the Middle East [17]. In another example, the RENATA study, which examined the use of palbociclib in Argentinian patients with hormone receptor-positive metastatic breast cancer, determined long-term treatment outcomes and treatment adherence. Specifically, the study results showed real-world progression-free survival (rw-PFS) of 36.7 months with first-line use of palbociclib. For this Argentinean population in the real-world setting, the RENATA study also demonstrated that palbociclib had lower incidences of dose interruption, delay, reductions and discontinuations in real-world settings, when compared with data from pivotal RCTs [18].

Treatment sequencing

RCTs can provide valuable information on efficacy and safety but are not always ideal for treatment sequencing because of high resource requirements. RWE studies offer a practical alternative in understanding treatment sequencing strategies based on examination of real-world treatment patterns and outcomes, without the expense and time needed for an RCT. A systematic review of global RWE studies conducted between 2015 and 2018 demonstrated that treatment with first-line abiraterone acetate, followed by enzalutamide, improved rw-PFS in patients with metastatic castration-resistant prostate cancer [31]. In the USA, RWE studies have been used to inform clinical decisions beyond first- and second-lines of treatment. A 2019 retrospective study demonstrated that first-, second- and third-line palbociclib treatment followed by subsequent hormonal therapy improved rw-PFS in patients with hormone receptor + and HER2- metastatic breast cancer [31]. In another study, Dhakal *et al.* demonstrated that a treatment sequence of everolimus following palbociclib-progression (first, second, third and fourth line) led to improved rw-PFS [32]. RWE studies have also been conducted in emerging economies to better understand treatment sequencing. In a 2019 Taiwanese retrospective study, investigators proved that treatment with first-line cetuximab followed by chemotherapy in second-line and bevacizumab in third-line lead to improved overall survival and clinical outcomes in patients with wild-type KRAS exon 2 mCRC [15].

Dosing strategy

RWE can help HCPs determine optimal dosing strategies that balance safety and effectiveness for specific patient populations. A patient's ethnicity may influence response to a therapy. In comparison to the USA and Europe, there is limited data around dosing of oncology treatments for patient populations in emerging economies. In a recent Asian RWE study, attenuated sunitinib doses were examined since prior research suggested the conventional dose (50 mg/day, 6-week cycles: 4 weeks on treatment, 2 weeks off treatment) was associated with high toxicities in Asian populations with metastatic renal cell carcinoma [13]. This study showed that the attenuated dose regimen of sunitinib (37.5 mg/d, 4 weeks of treatment, then 2 weeks of no treatment) had comparable real-world overall survival and rw-PFS, while significantly reducing toxicities as compared with the conventional doses [13].

AE management

RWE can guide clinical decision-making in the management of AEs. In a Chinese RWE study conducted in 2019, investigators examined real-world use of olaparib for treatment of advanced ovarian cancer in order to evaluate its safety and effectiveness. Findings identified several AEs during the follow-up stage such as abdominal distension, decreased blood pressure, increased body hair, burning, leg swelling and stomach sensations, which were unreported

Table 2. Identified structural and attitudinal barriers preventing adoption and use of real-world evidence in emerging economies.

Barriers		Contributing factors	Ref.
Structural	RWD availability	• Absence of commercially available secondary datasets outside of registries • Resource-intensive nature of RWD collection, management and analysis • Often times investigators are driving RWD collection	
	RWD quality	• Missing data • Data entry errors • Lack of data standardization	
	RWD integrity	• Data security breaches • Data governance not pervasive	
	Lack of regulator engagement	• RWE policy and applications not proactively addressed • Guidance on data standards and RWD credibility framework not issued • RWE not routinely considered for regulator decision making	[27]
Attitudinal	Entrenched HCP behaviors	• RWE studies unable to evoke similar level of confidence as RCTs • Culture and legacy training continue to govern clinical decision making	

HCP: Healthcare professional; RWD: Real-world data; RWE: Real-world evidence.

in earlier RCTs. The findings suggested that serious AEs can be effectively managed by dose reductions or temporary dose interruptions instead of treatment discontinuation [20].

Financial toxicity

RWE can help HCPs develop strategies that mitigate the effects of 'financial toxicity' associated with cancer treatment. This is especially important in emerging economies where patients may have reduced access to healthcare resources (e.g., healthcare insurance) and may be more vulnerable to high costs (direct and indirect) of medical care [22,33]. In a retrospective RWE study conducted in South Korea, investigators examined if nivolumab dose and scheduling could be modified to reduce financial toxicity among patients with non-small-cell lung cancer. Findings from this study suggested reduced nivolumab dose regimens maintained clinical effectiveness and could serve as an alternative treatment option in settings where financial toxicity may be prevalent [21].

Barriers preventing full use of RWE for clinical decision making

There are several barriers in emerging economies that prevent full use of RWE in oncology clinical decision making. These barriers are a result of structural and attitudinal factors that affect the way RWE is generated and utilized by healthcare stakeholders in emerging economies (Table 2). Key barriers identified include low availability of RWD, low RWD quality, RWD integrity issues, lack of regulatory engagement and entrenched HCP behaviors.

RWD availability

Experts confirmed that lack of commercially available secondary databases in emerging economies is perhaps the most acute contributing factor hindering widespread adoption of RWE. In the USA the Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009 led to the unlocking of EMRs as an RWD source [34]. Such legislation resulted in increased investment in healthcare IT and digitization of data. However, policy and legislation that may support RWE is either absent or in nascent stages in emerging economies. Furthermore, lack of such data collection hubs places the onus of RWD collection on practicing oncologists that are frequently leading studies without much technical support and sponsorship.

RWD quality

Lack of training and an understanding of data collection and entry methods can result in data missingness, errors and inconsistencies, thereby resulting in lower RWD quality. Additional factors that impact RWD quality in emerging economies include: the lack of regulatory RWE frameworks that promote data standards, and differences across data management systems (e.g., data structure, data format). Questionable RWD quality ultimately reduces the credibility of insights, resulting in mistrust of RWE [26].

Data integrity

Attacks on RWD are prevalent due to security vulnerabilities in emerging economies, further challenging a desired level of data integrity. For example, a Chinese regulatory (NMPA) report published in 2015 suggests data

manipulation in 30 RCTs conducted in China [35,36]. Beyond China, other countries in the Asia-Pacific region have also experienced breaches. In Latin America, 2.3 million health records of Mexican patients were breached in 2018 via inappropriate security protocols that opened access to identifiable patient information [37].

Entrenched behaviors

Entrenched physician behaviors and attitudes in oncology are generally prevalent on account of biases that physicians may have in viewing patient profiles and eligibility. In emerging economies, these behaviors, coupled with a conservative culture, play a role in impacting RWE adoption. At last, prior educational training focused on older therapies such as chemotherapy, accompanied by hesitancy of deviating from established treatment norms formed over decades of practice, may lower oncologist affinity to consider new therapies and treatment strategies [38,39].

RWE regulations

The voice of regulators is critical in creating momentum around RWE adoption and utilization. As discussed earlier, regulators in the USA and Europe have issued relatively detailed RWE guidance. In contrast, healthcare regulatory agencies in emerging economies, with the exception of China and Taiwan, are not markedly shaping the dialogue and definition around use of RWD/RWE [40,41,42]. This lack of regulatory guidance has resulted in an inertia for RWE research in emerging economies.

Call to action & future directives

Over the next 3–5 years, there is an opportunity for a societal contract in emerging economies to leverage RWE for oncology clinical decision-making. In particular, we propose three recommendations discussed below to catalyze the use of RWE in emerging economies.

Regulatory framework

Regulators in the emerging economies need to be engaged and play a proactive role as there is a critical need for RWE policy that accounts for regional considerations. Local RWE policy can be used to shape RWE dialogue and provide clear guidance on potential applications of RWE including for regulatory submissions. RWE policy guidelines also have the potential to promote rigorous data standards and governance procedures that can ultimately lead to improved data quality and integrity. Instituting policy will ultimately incentivize RWE adoption and build trust associated with use of RWE in emerging economies. As noted earlier, China and Taiwan are the only notable emerging economies that have provided RWE guidance in the public domain [40,41,42]. Consequently, it is no surprise that among the emerging economies, China and Taiwan have generated the largest share of RWE publications during the period of 2015 and 2019 (Figure 2; 803/1184 68%). Furthermore, health technology assessment (HTA) agencies in emerging economies also need to be engaged as these agencies impact how RWE may be utilized in clinical decision making for oncology. HTA guidance on RWE is established and robust in Europe. However, we are starting to see learnings from European HTA agencies applied to emerging economies such as Brazil and Argentina; and moving forward we expect HTA agencies to shape the dialogue even further.

RWE investments

Increased, systematic investments into RWD infrastructure (e.g., secondary databases, EMR, digital platforms) can be a cornerstone for accelerated local RWE generation. As stated earlier, lack of data standards and management is pervasive in emerging economies. Data integrity and manipulation are frequently cited issues, particularly in India and China [35,36,43,44]. Using widely accepted data standards and standard operating procedures such as those offered by the Observational Health Data Sciences and Informatics common data model, bring a structured approach to creating research ready, interoperable analytical data sets that may be used to power multiple studies. Data standardization needs to come hand-in-hand with clearly defined data governance rules, well-documented standard operating procedures and systems that ensure the strictest possible compliance. Together these investments are table stakes for setting up the foundation for RWE in emerging economies. In addition, there is an opportunity for the biopharma industry to collaborate with independent researchers to support data collection, statistical analysis and methods selected for RWE studies so that independent researchers are not conducting these in a silo.

RWE training

Even though oncology KOLs are driving the use of RWE in emerging economies, some oncologists remain unclear on how to best use RWE for clinical decision-making as well as how RWE is differentiated from RCTs. In such instances, RWE training imparted by KOL oncologists to oncologists practicing, both in community and center of excellence settings, can facilitate a paradigm shift from an RCT-only to an RCT-RWE hybrid insights model. Ideally, such training can be conducted through a train-the-trainer format and would begin with providing foundational RWE knowledge and progress to advanced topics such as innovative study designs and applications of RWE across the patient treatment journey. To execute RWE train-the-trainer programs, sponsors can take advantage of industry conferences such as International Society for Pharmacoeconomics and Outcomes Research China, European Society for Medical Oncology, Asia Congress, and oncology-specific medical conferences in emerging economies, such as the International Association for the Study of Lung Cancer Latin America Conference on Lung Cancer and the Asia-Pacific Gastroenterology Cancer Summit.

Conclusion

Despite RWE being a relatively nascent concept in emerging economies, we have seen evidence of increasing use over the past 5 years growing at 11% per year (Figure 2). That said, barriers specific to emerging economies need to be overcome through collaborative efforts, with regulatory agencies at the forefront. Regulatory engagement and sponsorship, RWE investments – both programmatic and one-off study sponsorships, and RWE training targeted at HCPs can harness the potential of RWE research in emerging economies.

Executive summary

Current scenario

- Increasingly, real-world evidence (RWE) is being used to guide clinical decision making in oncology in emerging economies. However, there are several challenges associated with RWE use in emerging economies.

Future directive

- The RWE challenges identified in this article can be addressed through regulatory engagement and sponsorship, RWE investments and RWE training targeted at healthcare professionals.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-0425

Author contributions

All the authors equally contributed in conceptualization, research, and analysis of the results of the manuscript. C Ghai and A Pangilinan helped in writing of the manuscript.

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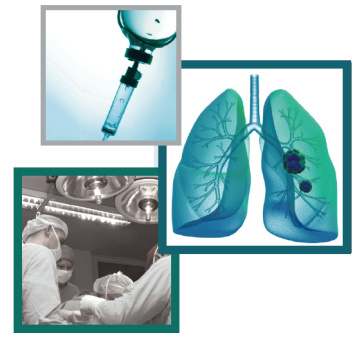

Use of immune checkpoint inhibitors in patients with solid tumors and pre-existing autoimmune or inflammatory disease: real-world data

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Aim: Immune checkpoint inhibitors (ICIs) are a cornerstone in cancer treatment but they can induce immune-related adverse events (irAEs). Furthermore, patients with pre-existing autoimmune and/or inflammatory disease (AID) have been excluded from clinical trials. The objective of this study is to evaluate the efficacy and safety of ICIs in patients with cancer and AID. **Materials & methods:** This is an observational, retrospective study carried out at the Medical Oncology Department of Hospital Universitario Puerta de Hierro, Majadahonda, Madrid between January 2016 and December 2018. **Results:** A total of 202 cancer patients treated with ICIs were included, 15 (7, 4%) of them had pre-existing autoimmune diseases. The most frequent pre-existing AID were thyroid diseases (33.3%): autoimmune hypothyroidism, Graves–Basedow disease and Hashimoto's thyroiditis. Three patients had psoriasis, two antinuclear antiboides + polyarthritis, one rheumatoid arthritis, another latent autoimmune diabetes in adults, another systemic lupus erythematosus and the last one, a polymyalgia rheumatica. In this series, the majority of patients (73.33%) did not experience any flare up of their autoimmune disease. In patients who had AID flare up, this was treated with corticosteroids. The most frequent cause of immunotherapy discontinuation was tumor progression (40%). A total of 20% of patients had to discontinue immunotherapy due to toxicity. **Conclusion:** In our series, AID flare ups or irAEs in patients with pre-existing AID who receive immunotherapy are not very common and can often be controlled without interrupting treatment. Prospective studies are needed to establish the incidence of irAEs in patients with pre-existing autoimmune conditions, evaluate risk–benefit and elaborate management clinical guidelines in this population.

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Keywords: cancer • discontinuation • flare-ups • immune-related adverse events • immune checkpoint inhibitors • immunotherapy • real-world data • risk–benefit • toxicity

Background

Immune checkpoint inhibitors (ICIs) have dramatically changed cancer treatment and have become standard of care in different types of cancer. ICIs include anti-programmed cell death 1 (anti-PD-1) agents (nivolumab and pembrolizumab), anti-programmed cell death-ligand 1 (anti-PD-L1) agents (atezolizumab, durvalumab and avelumab) and cytotoxic T lymphocyte-associated protein 4 inhibitors (anti-CTLA-4) like ipilimumab and tremelimumab. ICIs have been approved for the treatment of multiple advanced solid tumors, including melanoma, non-small-cell lung cancer (NSCLC) and urothelial cancer. In many other pathologies, these drugs are under investigation in other settings such as neoadjuvant and adjuvant treatments.

Ipilimumab, an anti-CTLA-4 antibody, was the first ICI approved by health authorities as a treatment for metastatic melanoma in patients without prior treatment, in 2011 [1]. After this, it has been studied in NSCLC or renal cell carcinoma. Ipilimumab was followed by antibodies that block PD-1 and PD-L1; the first of these was

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pembrolizumab, an anti-PD-1 antibody approved in 2014 for the treatment of metastatic melanoma [2] that was later also approved for NSCLC [3,4]. Nivolumab, another anti-PD-1, was initially approved for the treatment of melanoma [5], NSCLC [6,7] and renal cell carcinoma [8]. Atezolizumab is the only anti-PD-L1 and was approved in 2016 for the treatment of urothelial carcinoma [9]. Later, these PD-1/PD-L1 blocking antibodies have been shown to be effective in other types of tumors, such as head and neck cancer [10], Hodgkin lymphoma [11], hepatocellular carcinoma [12] or gastric cancer [13].

Since the mechanism of action is different, its combination has been studied and shown to have a synergistic effect, obtaining better results than monotherapy in melanoma. The combination of ipilimumab with nivolumab was approved by the US FDA in 2015 for the treatment of advanced melanoma [14] and has also been studied in the treatment of NSCLC with promising results [15]. The development of ICIs as a cancer treatment has brought with it the appearance of new toxicities, related to the activation of the immune system. These toxicities are known as immune-related adverse events (irAEs). The most frequent adverse effects are cutaneous, gastrointestinal, respiratory and endocrine (especially affecting the thyroid gland). These inflammatory and/or autoimmune manifestations are frequent, up to 70% for anti PD-1 and up to 90% for anti-CTLA-4. A recent meta-analysis has found that anti-CTLA-4 treatment causes high-grade irAEs in approximately 20–30% of patients [16]. Meanwhile, anti PD-1 treatment causes high-grade irAEs in less than 5% [17]. Due to the appearance of these irAEs, patients with autoimmune diseases (ADs) have been excluded from clinical trials with ICIs. For this reason, there is very little evidence about the impact that having a pre-existing AD can have on the selection, toxicity or efficacy of immunotherapy treatment.

Despite this, some studies show that although these patients often have exacerbations of their pre-existing AD, they can be easily managed, benefiting from the anti-tumor effect of ICIs. These studies, therefore, suggest that by balancing the overall risk–benefit, patients with pre-existing ADs can benefit from immunotherapy treatment.

The objective of this study is to evaluate the efficacy and safety of ICIs in patients with cancer and pre-existing autoimmune and/or inflammatory disease (AID).

Material & methods

Study design

This is an observational, retrospective and single-center study, carried out at the Medical Oncology Department of Hospital Universitario Puerta de Hierro, Majadahonda, Madrid. The list of patients was obtained through the HUPHM Pharmacy Service and it included all patients treated with immunotherapy (nivolumab, pembrolizumab, atezolizumab or ipilimumab) at the Medical Oncology Service of this hospital, between January 2016 and December 2018, inclusive. Inclusion criteria include all patients over 18 years old with a cancer diagnosis treated with immunotherapy according to assistential protocol or within a clinical trial.

Patients treated with different treatments (chemotherapy, tyrosin-kinase oral inhibitors) were excluded from our study. A total of 206 were reviewed (electronic medical record). Four had to be excluded because they did not meet the inclusion criteria.

Variables

Different variables were collected: age, sex, type of cancer, tumor stage, date of diagnosis, previous treatments, immunotherapy treatment, start date, end date, reason for discontinuation, immune-related adverse effects, date of last follow up or date of exitus.

Regarding the history of AD, the following data have been collected: type of AD, date of diagnosis, treatment and evolution of AD after treatment with immunotherapy.

Analysis

Statistical analysis was carried out using SPSS v25.

Results

A total of 206 medical records of patients treated with immunotherapy (nivolumab, pembrolizumab, atezolizumab or ipilimumab) were reviewed in the Medical Oncology Service, of the HUPHM, between January 2016 and December 2018, both years included. Of these, four were excluded because they did not meet the inclusion criteria, they had been treated with several immunotherapy drugs during the course of the disease and this could confound our results. Of the 202 patients diagnosed with cancer and treated with immunotherapy (monotherapy or in

Table 1. Characteristics of patients with previous autoimmune disease.

Patient	AID	Tumor	ICI	Line of treatment	Treatment duration	Discontinuation	Evolution AID	Exitus
1	Autoimmune hypothyroidism	Renal cell carcinoma	Atezolizumab	2	9 weeks	Toxicity	Exacerbation	No
2	Autoimmune hypothyroidism	Hepatocarcinoma	Nivolumab	1	4 weeks	Toxicity	No changes	Yes
3	Graves–Basedow disease	Lung cancer: adenocarcinoma	Pembrolizumab	1	6 weeks	Progression	No changes	No
4	Graves–Basedow disease	Hepatocarcinoma	Nivolumab	2	15 weeks	Exitus	Exacerbation	Yes
5	Hashimoto thyroidis	Melanoma	Nivolumab + ipilimumab	1	33 months		No changes	No
6	Psoriasis	Lung cancer: adenocarcinoma	Nivolumab	1	12 months	Toxicity	Exacerbation	No
7	Psoriasis	Lung cancer: adenocarcinoma	Nivolumab + carboplatino/paclitaxel	1	14 months		No changes	No
8	Psoriasis	Lung cancer: squamous cell carcinoma	Nivolumab	1	12 months	Progression	No changes	No
9	ANA + polyarthritis	Lung cancer: adenocarcinoma	Pembrolizumab	1	6 weeks		Exacerbation	No
10	ANA + polyarthritis	Timoma	Pembrolizumab	2	3 weeks	Progression	No changes	Yes
11	Rheumatoid arthritis	Lung cancer: adenocarcinoma	Nivolumab	2	14 months	Exitus	No changes	Yes
12	LADA	Melanoma	Nivolumab + ipilimumab	5	13 weeks	Progression	No changes	No
13	Systemic lupus erythematosus	Renal cell carcinoma	Nivolumab	2	7 months	Progression	No changes	No
14	Polymyalgia rheumatica	Hepatocarcinoma	Nivolumab	1	18 months		No changes	No
15	Antinuclear antibodies+ (ENA, DNA)	Hepatocarcinoma	Nivolumab	1	8 months	Progression	No changes	Yes

AID: Autoinflammatory disease; ANA: Antinuclear antibody; ENA: Extractable nuclear antigen; ICI: Immune checkpoint inhibitor; LADA: Latent autoimmune diabetes in adult.

combination) at a certain point in the course of their disease, 15 were found to have a history of AD (7.4%). The characteristics of these 15 patients are described in Table 1.

A broad spectrum of pre-existing AD was reported. A total of five patients (33%) had a history of autoimmune thyroid disease, two (13%) patients had a history of autoimmune hypothyroidism, two (13%) of Graves Basedow disease and one (7%) of Hashimoto thyroiditis. A total of three (20%) patients had psoriasis, two (13%) antinuclear antiboides (ANAs) + polyarthritis, one (7%) rheumatoid arthritis, one (7%) latent autoimmune diabetes in adults Type diabetes, another systemic lupus erythematosus and another, polymyalgia rheumatica. The last case was a patient with positive ANAs but without established diagnosis.

Most of the patients (73.33%), did not experience any change or exacerbation of their AD during immunotherapy treatment, four (27%) of them had a worsening of prior manifestations.

The most frequent cause of discontinuation of immunotherapy treatment was the progression of tumor disease (40%), five patients of them died (33.3%). Only three of the 15 patients (20%) had to discontinue immunotherapy due to toxicity. In two of these patients, the toxicity was related to a worsening of prior manifestations of the pre-existing AD (psoriasis in one case and autoimmune hypothyroidism in another), while the toxicity of the third patient, hepatotoxicity, was not related to his underlying AD (autoimmune hypothyroidism).

Finally, it is important to note that five of the 15 patients (33.3%) did not present any immune-related adverse reaction, although two of these five patients experienced a worsening of their underlying disease.

Of the 202 patients, 114 (56.4%) experienced some irAE. Of those, 58 (50.9%) experienced only one, 33 (28.9%) experienced two and 23 (20.2%) experienced three or more (up to six).

Because, the degree of toxicity was not well recorded in the medical records in all cases, we considered serious irAEs those requiring hospital admission and/or interruption of immunotherapy treatment. Of the 114 patients

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Table 2. Immune-related adverse events.

irAEs	Nivolumab (n = 124)	Pembrolizumab (n = 26)	Atezolizumab (n = 10)	Ipilimumab (n = 5)	Nivolumab + ipilimumab (n = 24)	Nivolumab + daratumumab (n = 6)	Nivolumab + carboplatino/paclitaxel (n = 7)
Asthenia	22 (17.7%)	12 (46.2%)	0	0	2 (8.3%)	1 (16.7%)	3 (42.9%)
Hyporexia	1 (0.8%)	3 (11.5%)	0	0	0	0	0
Rash	4 (3.2%)	2 (7.7%)	1 (10%)	2 (40%)	5 (20.8%)	0	2 (28.6%)
Pruritus	6 (4.8%)	4 (15.4%)	0	0	6 (25%)	1 (16.7%)	2 (28.6%)
Vitiligo	1 (0.8%)	0	0	0	1 (4.2%)	0	0
Psoriasis	1 (0.8%)	0	0	0	1 (4.2%)	0	1 (14.3%)
Infusional reaction	1 (0.8%)	0	0	0	1 (4.2%)	0	0
Diarrhea/colitis	3 (2.4%)	4 (15.4%)	0	0	4 (16.7%)	0	0
Nausea/vomiting	2 (1.6%)	1 (3.8%)	0	0	0	0	1 (14.3%)
Liver toxicity	9 (7.3%)	2 (7.7%)	1 (10%)	0	6 (25%)	0	0
Pancreatic toxicity	3 (2.4%)	0	0	0	1 (4.2%)	0	0
Pneumonitis	7 (5.6%)	2 (7.7%)	0	0	5 (20.8%)	0	0
Arthritis	5 (4%)	3 (11.5%)	1 (10%)	0	0	0	1 (14.3%)
Neurotoxicity	5 (5%)	1 (3.8%)	0	0	0	0	0
Anemia	2 (1.6%)	1 (3.8%)	0	0	0	0	0
Neutropenia	3 (2.4%)	2 (7.7%)	0	0	0	0	0
Thrombopenia	1 (0.8%)	1 (3.8%)	0	0	0	0	0
Renal toxicity	1 (0.8%)	1 (3.8%)	0	0	2 (8.3%)	1 (16.7%)	0
Thyroid toxicity	16 (12.9%)	2 (7.7%)	1 (10%)	0	3 (12.5%)	1 (16.7%)	1 (14.3%)
Parathyroid toxicity	1 (0.8%)	0	0	0	0	0	0
Mellitus diabetes	0	1 (3.8%)	0	0	2 (8.3%)	0	0
Suprarrenal insufficiency	1 (0.8%)	0	0	0	1 (4.2%)	0	0
Others	3 (2.4%)	0	0	0	2 (8.3%)	0	1 (14.3%)

irAE: Immune-related adverse event.

who presented any irAEs, 24 had to discontinue immunotherapy (11.9%). Of these 24 patients who had severe irAEs, 12 were receiving nivolumab as monotherapy and seven nivolumab + ipilimumab.

Table 2 shows the different irAEs that appeared with the different treatment schedules.

Discussion

ICIs represent an important new treatment modality for cancer patients. Despite the important clinical benefits of ICI therapy, these treatments can also cause a variety of irAEs. The mechanisms leading to irAEs are unclear, although irAEs caused by ICIs resemble AD. That is the reason why all the clinical trials leading to the approval of ICI therapy actively excluded patients with pre-existing active AD because of apprehension that these individuals might be at risk for treatment-induced irAEs.

The management of irAES according to the European Society for Medical Oncology guidelines depends on the grade. For grades 3 and 4, immunotherapy has to be permanently discontinued. Treatment with high-dose corticosteroids should be started promptly and other immunosuppressive treatments such as infliximab, micofenolato or ciclofosfamide should be considered, in case of deterioration under steroids. In grade 1 toxicity, immunotheray can be continued adding other treatments for the toxicity. In grade 2, treatment is usually discontinued, corticosteroids can be started and treatment can be resumed, if toxicity improves under treatment [18].

Combination immunotherapy has only been approved for patients with metastatic melanoma. Treatment-related AEs were observed in 95% of patients. In 55% of patients, these AEs were of grade 3 or higher [19] The onset of grade 3–4 toxicities for either monotherapy with nivolumab or combination immunotherapy differs, as irAEs not only may develop earlier in combination therapy but also may start over a prolonged period of time.

The objective of this observational study of patients with cancer and pre-existing AD is to evaluate the efficacy and safety of ICIs.

Many patients who are diagnosed with cancer have a pre-existing AD, for example, approximately 14–25% of patients with lung cancer also have an AID [20]. However, in our series only 7.4% of patients with cancer treated with ICIs had a pre-existing AID. This low prevalence in our sample may be due to several factors. First, the use of immunotherapy in patients with pre-existing AD is not very widespread due to the lack of experience. The increased risk of irAEs, which can be unpredictable and potentially very serious, and the risk of AID symptom exacerbation (flare-ups) in patients with pre-existing AID has led these patients to be frequently excluded from immunotherapy clinical trials. For this reason, there is very little evidence and very little clinical experience in the use of immunotherapy in these patients. Second, our sample includes patients receiving immunotherapy within a clinical trial, whose exclusion criteria include suffering or having some autoimmune-based pathology.

In our study, we found that four of the 15 patients (26.67%) with pre-existing AID had autoimmune exacerbations. This percentage was lower to that observed in other series. Johnson *et al.* [21] retrospectively evaluated 30 patients with pre-existing autoimmune disease and metastatic melanoma. Of the 30 patients who received ipilimumab, 15 (50%) experienced irAEs or flare ups of their underlying AD. Leonardi *et al.* [20] retrospectively analyzed the safety of anti-PD-1 and PD-L1 antibodies (nivolumab, pembrolizumab or atezolizumab) in 56 patients with NSCLC and pre-existing AD. A total of 55% of patients developed a flare up and/or irAEs. Danlos *et al.* [22] compared 45 patients with underlying AD to 352 patients without AD who were treated with anti-PD-1 agents in the Registry of Severe Adverse Reactions to Immunomodulatory Antibodies Used in Oncology between 2014 and 2016. About 47.1% of the patients with AD experienced an AD flare up, 65.9% experienced an irAEs and 9.4% developed a grade 3/4 irAEs. In a recent review of 41 case reports published to date, in 65.6% of patient immunotherapy resulted in a flare up of the baseline disease; being severe and very severe in 22.7% of patients [23].

Of the four patients in our study with pre-existing AID that had flare ups, one was treated with atezolizumab, two with nivolumab and one with pembrolizumab, so we cannot think that a certain drug could interfere with previous AID more than another.

The most frequent cause of discontinuation of immunotherapy was not irAEs, as we might expect from patients with pre-existing AID, it was progression of tumor disease (40%). Only three of the 15 patients (20%) had to discontinue immunotherapy for toxicity. Despite the fact that five patients died during our follow-up period, no deaths occurred as a consequence of treatment.

On the other hand, although it is true that irAEs occurred (not related to pre-existing AID) in ten of the 15 patients (66.7%), most were mild and easy to control. Of the five patients (33.3%) who did not have any irAEs, two experienced worsening of their disease. Three patients (20%) did not present any irAE or not to their pre-existing AID. The incidence of irAEs observed in Johnson *et al.* did not exceed the incidence of irAEs found by other studies in a population without AID. In our study, 66.7% of patients with AID present irAEs.

Despite the limited information in this regard, some studies have concluded that ICIs can be used in patients with previous AID, since the potential risks do not seem to outweigh the benefit of these treatments.

Khan *et al.* [24] observed that AID were relevant in NSCLC, 14% of patients with NSCLC had a concurrent AID and they could be treated with ICIs, since they observed that patients with AID present a mortality from cancer and from any cause similar to those patients who do not have AID. In patients with melanoma and AID, Johnson *et al.* [21] concluded that ipilimumab treatment can be considered, always leading to close surveillance and monitoring of the patient, and the Menzies *et al.* study obtained a similar conclusion regarding anti-PD1 therapy [25].

This is a complex topic and our series is very heterogeneous with different types of tumors and different types of immunotherapy treatments described. Complex interactions could happen between all the conditions presented. Great caution must be taken before drawing conclusions as some combinations of cancer with AID may respond remarkably well and other subsets of patients may only accrue harm.

Conclusion

In our series, exacerbations or irAEs in patients with prior AD receiving immunotherapy treatment are not very common and can often be controlled without interruption of treatment. Administration of immunotherapy in cancer patients with a pre-existing controlled autoimmune condition seems safe with an adequate follow up and early onset of treatment once flare ups or irAES happen.

Prospective studies are needed to establish the incidence of irAEs in patients with pre-existing autoimmune conditions, evaluate the risk–benefit indexes and elaborate management clinical guidelines in this population.

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Summary points

- Immune checkpoint inhibitor have dramatically changed cancer treatment and have become standard of care in different types of cancer.
- The development of immune checkpoint inhibitors as a cancer treatment has brought with it the appearance of new toxicities, immune-related adverse events.
- The most frequent adverse effects are cutaneous, gastrointestinal, respiratory and endocrine (especially affecting the thyroid gland).
- There is very little evidence about the impact that having a pre-existing autoimmune disease (AD) can have on the selection, toxicity or efficacy of immunotherapy treatment.
- By balancing the overall risk–benefit, patients with pre-existing ADs can benefit from immunotherapy treatment.
- Most of the patients (73.33%), did not experience any change or exacerbation of their AD during immunotherapy treatment, four (27%) of them had a worsening of prior manifestations.
- The most frequent cause of discontinuation of immunotherapy treatment was the progression of tumor disease.
- Administration of immunotherapy in cancer patients with a pre-existing controlled autoimmune condition seems safe with an adequate follow up and early onset of treatment once flare ups or immune-related adverse events happen.

Author contributions

V Calvo analyzed and interpreted the patient data regarding the autoimmune diseases and the adverse events and wrote the article. MA Fernández collected all the data. A Collazo-Lorduy was a major contributor in writing the manuscript. F Franco contributed to the clinical interpretation of data. B Núñez collected data and helped with the writing. M Provencio contributed to the design and final interpretation. All authors read and approved the final manuscript.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that both data collection and analysis have been carried out anonymously at all times, taking appropriate precautions to maintain patient confidentiality. When patients entered the Medical Oncology Department (Hospital Universitario Puerta de Hierro, Majadahonda, Madrid) they signed a document allowing us to use their electronic medical records for research purposes. This work has been classified by the Spanish Agency of Medicines and Health Products (AEMPS) as a postauthorization study with other designs different from the prospective follow up (abbreviated as EPA-OD), and has the favorable opinion of the Ethical Committee for Research with Medicines of the HUPHM and the Ethics Subcommittee of the Autonomous University of Madrid. Institutional consent for publication was obtained.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Review

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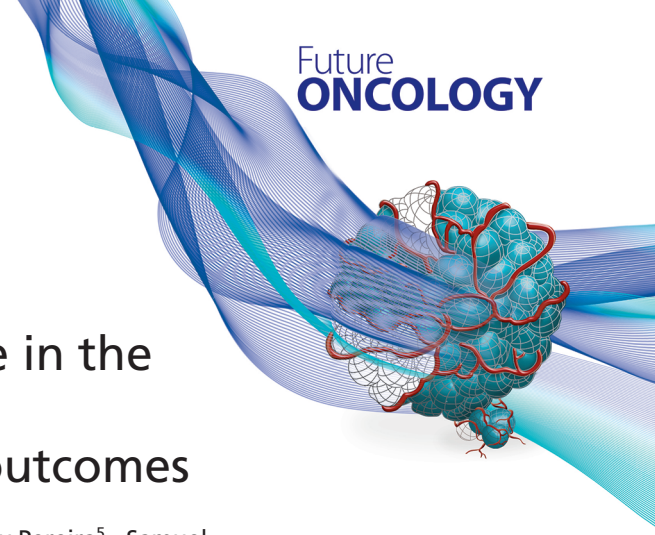

Evolving use of real-world evidence in the regulatory process: a focus on immuno-oncology treatment and outcomes

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In recent years, regulatory bodies have increasingly recognized the utility of real-world evidence (RWE) for supplementing and supporting clinical trial data in new drug applications. Nevertheless, the integration of RWE into established regulatory processes is complex and the generation of 'regulatory-grade' real-world data faces operational, methodological, data-related and policy-related challenges. In parallel with this evolving role for RWE, immuno-oncology therapies have emerged as leading cancer treatments and are expected to continue to play a central role in the future. In this article, we review the current literature on the use of RWE for regulatory submissions, with a focus on novel anticancer immunotherapies, and discuss the utility and current limitations of RWE in the context of drug development and regulatory approvals.

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Over the past several decades, increasingly complex drug approval processes overseen by authorities such as the US FDA and the EMA have necessitated concerted efforts to accelerate and reduce the cost burden of regulatory decision-making, which includes a move toward a defined integral role for real-world evidence (RWE) within regulatory approval processes [1–4]. Although data from randomized controlled trials (RCTs) remain standard for new drug evaluations, there are situations where a robust clinical trial is not practicable, for example, because of low recruitment prospects (e.g., for rare diseases), prohibitive anticipated costs and/or resource needs or ethical prohibition (e.g., in cases where there is no established standard of care [SoC] and an RCT would be unethical) [5–9]. Moreover, the clinical trial process is time consuming, which could delay availability of new effective treatments. In these circumstances, innovative approaches are needed to assess the benefits and risks of a medication. One such approach is to use real-world data (RWD) to help highlight unmet medical needs and demonstrate the effectiveness, tolerability and patterns of care of a given pharmacological agent in real-life settings and populations (Table 1) [2,3].

RWD sources are varied, and include electronic health records (EHRs), medical and pharmacy claims and billing, and product and disease registries, as well as patient-generated data (e.g., from in-home-use settings) [1,2]. Moreover, in the era of social media and availability and use of smartphones and tablets, data can be collected directly from patients using these tools. RWE represents information on usage patterns and potential benefits or risks of a medical product derived from analyses of these RWD [1]. By their nature, RWD can be more generalizable than those obtained from RCTs; in large part, this stems from the need for RCTs to control for variability [10] and to ensure strong internal validity, a requirement for robust efficacy assessment. By contrast, real-world studies may allow more permissive inclusion criteria, and accordingly may have fewer restrictions on patient characteristics and co-morbidity profiles, with commensurate enhancements in generalizability or external validity.

Table 1. Utility of real-world evidence in drug development and regulatory approvals.

Stage of drug development	Application of real-world evidence
Preapproval	• Highlight diseases not currently served by existing treatments and current unmet needs • Help understand a potential role in the therapeutic approach • Facilitate clinical trial design and acceleration of novel therapies by characterizing patient populations in need
Peri-launch (just before and immediately after marketing approval)	• Estimate treatment effect • Allow comparisons between real-world treatment effectiveness and efficacy from clinical trial data • Contribute to knowledge of patient safety • Inform clinical trial design and appropriate end point usage • Describe patient populations (e.g., characterize patients in underpowered subgroup analyses) • Act as external control for single-arm clinical trials

Questions about the effectiveness and safety of a new drug in real-world populations may be particularly important when clinical trial results lead to dramatic shifts in SoC for broad groups of patients. In the past 10 years, the advent of immuno-oncology (I-O) therapy has transformed the treatment landscape for numerous solid tumors and hematologic malignancies, and the emergence of novel agents harnessing the host immune system will likely continue on an upward trajectory for the foreseeable future [11–13]. In this constantly evolving environment, developers and regulators confront unique questions and drive critical developmental and regulatory processes that could be informed by RWE. In this article, we review current literature on the use of RWE in regulatory processes, with a focus on I-O therapy as a highly topical example of a relatively new and emerging class of treatments. We also discuss the utility and current limitations of RWE in the context of regulatory approvals and include select case studies to illustrate challenges of generating 'regulatory-grade' data from analyses of patients receiving I-O therapy in real-world settings.

RWE & regulatory assessments of new therapies

Historically, the role of RWE in regulatory processes has been to supplement existing approvals, and not as a central component of initial drug applications. RWD were most frequently employed for postmarketing assessment of safety, for risk management or for assessment of benefit–risk across the drug life cycle [14]. RWE were also used to support new indications for approved medications; an early example from the I-O field being the 2013 EMA decision to extend the indication for ipilimumab (a cytotoxic T-lymphocyte-associated protein 4 inhibitor) to include previously untreated adults with unresectable or metastatic melanoma, which was based on data from both clinical trials and retrospective observational studies [15]. Infrequently, RWE has supported initial drug approvals, primarily in rare-disease and/or oncology settings. In these situations, RWD on historical clinical outcomes were drawn from chart reviews, expanded access programs, rare-disease registries and other clinical practice settings. Although not always the case, these RWD typically supported clinical data from interventional trials for which a control arm was infeasible or unethical and where a large effect size was expected based on initial data [1].

Early examples of RWE supporting new drug approvals include the 2006 and 2010 FDA accelerated approvals of Genzyme's alglucosidase alfa formulations for Pompe disease, a rare multisystem genetic disorder, which relied on comparison of clinical trial data with data from historical controls from a multinational disease registry [16,17]. In the oncology setting, an early example was the 2014 FDA accelerated approval of Amgen's blinatumomab for Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia, which included a comparison of data from a single-arm clinical trial with data from matched historical controls using propensity score methods [18–20]. More recent examples include the 2016 EMA approval of MolMed SpA's Zalmoxis, an immune-gene therapy for rare high-risk hematologic malignancies, which used historical data from the European Bone Marrow Transplantation patient registry [21], and the 2018 FDA approval of Fresenius Kabi AG's lipid emulsion fish oil triglycerides for pediatric patients with parenteral nutrition-associated cholestasis, which also used matched historical controls [22]. While this acceptance of RWE as supportive of new approvals is noteworthy, a frequent postmarketing requirement was that the clinical benefit be confirmed in an RCT [16,19,23].

Harnessing RWD to provide evidence for regulatory decision-making pose various operational challenges, including those related to feasibility (e.g., ease and cost of data access), governance (e.g., impact of the data source's data-sharing policy in relation to sponsored research) and sustainability (e.g., durability of data collection and analysis) [14]. Another operational challenge relates to governmental/regional policies that may limit data sharing and access to real-world patient data, such as the US Health Insurance Portability and Accountability Act and

Table 2. Methodological and data-related challenges to the use of real-world evidence in regulatory decision-making.

	Challenge
Methodological	• Assignment of treatment based on physician judgment rather than randomized allocation may hinder establishment of a causal relationship between treatment use and clinical outcome • Unobserved confounders (e.g., physician choice, patient preference, unmeasured health risks or differential access to treatment) • Absence of universally accepted methodological standards for study design and data reporting • Lack of investigator expertise in real-world data generation and analysis • Achieving a sample size required to determine treatment efficacy • Different behavior in real-world studies versus clinical trials (e.g., the Hawthorne effect) due to differences in monitoring frequency • Logistics of engaging healthcare systems to collect usable real-world data
Data related	• Management of missing/incomplete data and follow-up • Consistency and accuracy of data collection and recording (including data on potential confounders and effect modifiers) • Possibility of data manipulation resulting from retrospective nature of data collection • Risk of false positives as a result of under-reported multiple testing/reporting bias • Establishing validity of patient-generated data (i.e., sources outside of the healthcare environment) • Underestimation of patient safety concerns

the new General Data Protection Regulation in the European Union. Potential solutions to this challenge have been suggested, at least in the USA, including establishment of dedicated policy on patient privacy that would be overseen by the US government or an independent, nonprofit organization [24].

Even when operational barriers are overcome, generation of RWE is subject to various methodological and data-related challenges, as summarized in Table 2. A major limitation of RWD is that assignment of treatment based on physician judgment rather than randomized allocation may hinder establishment of a causal relationship between treatment use and clinical outcome [1]. Unobserved confounders (e.g., physician choice, patient preference, unmeasured health risks or differential access to treatment) can also influence outcomes of real-world research, whereas these factors are generally addressed by randomization in traditional clinical trials [3]. Additionally, under certain circumstances, it can be challenging to achieve a suitable real-world sample size to allow robust statistical analysis [25]; this is notable in oncology, where treatments increasingly target smaller subsets of patients, often defined by a genetic mutation. Other limitations of RWE include but are not limited to the challenges of identifying and defining reliable clinical end points in claims data, lack of follow-up and reliability in patient registries, and missing/incomplete data [26]. Indeed, the need to account for missing/incomplete data is a common challenge in real-world studies, both in the context of data that should be available but are often missing (e.g., performance status) and data that are generally not collected in routine clinical practice (e.g., history of co-morbidities, date of disease progression, etc.). The resultant level of uncertainty in terms of patient history is a particular issue for EHRs and administrative records, where there may be less granularity on the phenotypic status of patients, thus necessitating assumptions or proxy measurements to infer disease status [3].

There is increasing recognition of the need to address these limitations in order to increase confidence in RWE and ensure that the evidence is of 'regulatory-grade' quality. This includes research to develop specific real-world end points, such as a composite real-world mortality end point, a potential proxy for overall survival (OS) [27] and efforts to establish a systematic approach to improve comparisons between randomized trials and observational studies [28,29]. Additionally, this may involve larger initiatives designed to develop rigorous study designs and statistical methodologies and to standardize methods, several of which are underway in Europe and the USA. For example, the FDA-funded DUPLICATE initiative aims to replicate the results of RCTs using RWD, such as from claims databases, with the ultimate objective of exploring whether RWE aligns with clinical trial data [30,31]. Another, the Innovative Medicines Initiative, a public–private consortium comprising industry, academia, Health Technology Assessment agencies and regulators, has launched the GetReal (2013) and GetReal Initiative (2018) projects with the overall aim of assessing how robust new methods of RWE collection and synthesis could be developed and considered for adoption earlier in pharmaceutical research and development and the healthcare decision-making process [32]. Finally, the establishment of a pan-European integrated and sustainable network of real-world databases – the Data Analysis and Real World Interrogation Network (DARWIN) – that will access and analyze healthcare data of verified quality and content has been identified as a top priority by the joint Big Data Task Force of the EMA and the Heads of Medicines Agencies network [33]. With increased understanding of the potential value of RWE in driving regulatory decisions, these efforts and initiatives offer opportunities to highlight related challenges and potential solutions.

Impact of RWE on regulatory policy

In 2016, the 21st Century Cures Act stipulated that the FDA considers the use of RWE in support of new indications for approved drugs and biologics, or to help address postapproval requirements. This was followed by the 2018 publication of the Framework for FDA's Real-World Evidence Program [1]. This program seeks to assess the utility of RWD for supporting changes to approved indications or assessing comparative effectiveness and safety of a licensed drug. The program will focus on addressing three key issues: whether the RWD are fit for the intended application; whether the trial or study design used to generate the RWD provides adequate scientific evidence to answer or help answer regulatory questions, and whether the study conduct meets FDA regulatory requirements, such as for study monitoring or data collection [10]. As a follow-up, the FDA published additional guidance for industry in 2019 on the process for submitting RWE as part of regulatory filings [34]. The 2018 FDA framework and subsequent guidance for industry represent nonbinding recommendations put forward while the FDA continues to explore approaches to optimize the utility of RWE. In Europe, the EMA and European Commission initiated the Adaptive Pathways approach in 2014 as a mechanism for allowing RWD to support regulatory submissions, and related guidance for industry followed in 2016 [35,36]. European regulators also continue to work toward integration of RWE within the existing regulatory system through ventures such as the aforementioned Innovative Medicines Initiative and DARWIN platform [37]. Importantly, external stakeholders from academia and industry will be instrumental to the FDA and EMA in determining whether RWE can be applied as a tool for future primary decision-making [2,10]. Further draft guidance on using RWE in the FDA regulatory process is expected to be published in December 2021 [38].

Although regulatory bodies are beginning to establish frameworks and guidance for use of RWE in their decision-making, and efforts are underway to formalize standards and methodology for generating RWE, there remains a lack of clarity on what constitutes 'regulatory-grade' RWE. The importance (and difficulty) of generating acceptable evidence has been highlighted in recent negative feedback from the FDA on some RWE submissions, centering on criticisms of the representativeness of real-world populations, data quality and potential bias (re: small sample sizes, missing/incomplete data, confounding factors, misclassification issues and selection bias) [38]. This may be further compounded by possible differences in definitions of 'regulatory-grade' depending on the end user (e.g., data for analysis of real-world clinical effectiveness vs data for real-world economic analysis) and the hypothesis, based on early results from the DUPLICATE initiative, that utility of RWE for replicating clinical trial results may depend on the therapy area and comparators utilized [31]. This lack of clarity on 'regulatory-grade' RWE stems, at least in part, from regulatory approvals and rejections that are nearly always communicated with no direct indication of the relative importance of the provided evidence in that decision. A recent example of this can be seen with the successful extension of the approved indications for palbociclib to include male patients with advanced or metastatic breast cancer. Although the associated multidiscipline review document and a related publication provided useful feedback on the strengths and weaknesses of the performed real-world analyses, highlighting several methodological limitations and related concerns regarding definitive evidence [39,40], the documents ultimately conclude that the RWE were supportive of the submission. Thus, while the submission was successful, it is unclear whether the submitted RWE was considered 'regulatory-grade' or whether it was necessary at all (i.e., the submission would have been approved without it). Indeed, experience suggests that the current RWE submission process may be more a case of 'policy by precedence versus policy by direction' – the industry draws on the apparent merits of previous submissions, rather than being specifically directed by the regulatory bodies to provide the information they require. This suggests a need for increased communication between regulatory bodies and those submitting data packages, particularly regarding exactly what is required from the RWD for the related evidence to inform their decisions. Moreover, these discussions will also provide a forum for agreement on other aspects related to quality of submitted RWE, for example, what criteria need to be met to establish a synthetic control or comparator arm using RWD. There is hope that future guidance from the regulatory bodies, building on the existing frameworks, will provide much-needed clarity on what is required for RWE to be considered 'regulatory grade.'

RWE & the regulatory assessment of I-O agents

Immunotherapy for cancer is a rapidly expanding therapeutic area, as demonstrated by the 91% increase in the number of active or investigational I-O agents introduced worldwide and 31 FDA drug approvals over the past 2 years [13]. Immune checkpoint inhibitors targeting the PD-1/PD-L1 axis, for example, have become SoC for no less than 16 cancer types and tissue-agnostic indications [41]. Compared with conventional treatments, immune checkpoint inhibitors have demonstrated significantly greater efficacy and durability of response in patients with

a wide range of cancers [42]. It is also evident from reported development pipelines that the number of I-O agents will further increase; for example, more than 1800 I-O agents are currently in development in the USA alone [13].

The fast-changing and expanding I-O treatment landscape highlights the need to better inform treatment decisions through rapid assessment of how new therapies affect patient outcomes. As discussed previously, clinical trials are the established mechanism for such assessments, but they can take a long time to conceive and conduct. Indeed, while the usual length for a Phase III trial is 1–4 years [43], many clinical trials experience significant delays to recruitment, which often leads to a further increase in the length of the study [44]. Since many new I-O agents address significant unmet medical needs, the time required to develop a trial protocol, recruit patients and conduct a clinical trial might be seen as an unacceptable delay to patients accessing new and effective treatments. Moreover, clinical trials for orphan drugs (i.e., those targeting rare diseases), where unmet medical needs may be greatest, on average take nearly twice as long as trials of nonorphan drugs [45]. This is a major consideration as I-O therapies are increasingly being extended to smaller patient populations with rarer conditions. Even in the case of less-rare cancers, recruitment into later-stage I-O studies (i.e., Phase III RCTs) can be challenging as data from earlier studies may be robust enough that investigators feel that clinical equipoise has been lost and are reluctant to enroll into larger trials where SoC has already been surpassed. In addition, patterns of response with I-O therapies are somewhat distinct from other cancer treatments and are often characterized by durable tumor suppression and associated long-term survival. This has led to calls for innovative methodologies and study designs [46,47], suggesting that traditional clinical trial approaches may not be optimal for assessing long-term effects of I-O therapy. A further consideration is the large number of emerging I-O agents [13]. This rapid expansion may result in a need to compare new agents and new combination regimens against each other and/or against an expanding list of SoC treatments. However, conducting multiple RCTs to facilitate these comparisons may be cost and resource prohibitive. In this environment, there is a strong case for increased acceptance on the part of regulatory bodies to submissions based on limited clinical trial data supplemented with RWD.

Over the past few years, there have been multiple examples of RWD sources rapidly providing valuable data on the impact of newly licensed I-O therapies, particularly in the context of assessing the generalizability of effectiveness and/or tolerability to broad patient populations [48–53], or specific populations usually excluded from clinical trials [50,54,55]. These postapproval data extend our overall understanding of the efficacy and safety profiles of new I-O therapies. However, as discussed earlier, the increased general acceptability of RWE in the context of regulatory filings and the expected need for RWD to contribute to I-O regulatory submissions indicate an important preapproval role for RWE in the emerging I-O field. In the next section, we present four illustrative cases in which RWE on I-O treatments and outcomes were used to support regulatory submissions. By necessity, we were compelled to focus on those cases with publicly available information on both the analyses and the associated regulatory submission and, as such, we may have omitted other relevant examples. Nevertheless, the following cases, which we consider to be appropriate 'archetypal' use cases highlight some of the common methodological and data-related challenges associated with the use of RWE in the regulatory process.

Using RWE for an initial drug approval

In September 2017, the European Commission granted marketing authorization for the PD-L1 immune checkpoint inhibitor avelumab as monotherapy for adults with metastatic Merkel cell carcinoma (MCC), primarily on the basis of data from the single-arm JAVELIN Merkel 200 clinical trial [56–58]. Before approval of avelumab, there was no established SoC for patients with this rare aggressive skin cancer, and most received one of several available chemotherapy regimens. Although JAVELIN Merkel 200 indicated the clinical activity of avelumab in metastatic MCC, the trial did not include a comparator arm. As such, a retrospective, observational study was conducted to provide data on outcomes of patients with metastatic MCC receiving chemotherapy regimens in clinical practice, which could then be compared with JAVELIN Merkel 200 data [56].

The observational study included 34 patients in Europe and 87 in the USA, with the latter divided into two cohorts comprising 67 patients who received first-line chemotherapy and 20 who received second- or later-line chemotherapy [56]. Naive, unadjusted clinical outcomes data from these patients were then compared with outcomes data from the JAVELIN Merkel 200 trial [59].

There were several methodological challenges associated with the comparison of data from JAVELIN Merkel 200 and the observational study. First, sample sizes were small, with 88 patients in the clinical trial and 67 first-line and 54 second- or later-line patients in the observational study. Second, while the patient populations were generally comparable, there were noteworthy imbalances. For example, 56% of patients in JAVELIN Merkel 200 had an

Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 and 44% had an ECOG-PS of 1. Among patients with available ECOG data in the observational study, only 21% had an ECOG-PS of 0 and 12.5% had an ECOG-PS of 2 or 3. Furthermore, the observational study included immunocompromised patients (22% were immunocompromised) who were excluded from JAVELIN Merkel 200 [56]. It is noteworthy that the observational study population was split into 'immunocompetent' and 'all-qualified' subgroups for comparison with JAVELIN Merkel 200 data, which helped assuage concerns about the impact of immunosuppression on efficacy outcomes. However, this process further reduced the size of comparable samples, likely further impacting statistical reliability. An additional limitation relates to missing/incomplete data in the observational study. For example, 15 of the 87 US patients (~17%) and all 34 of the European patients had no ECOG-PS data. Interestingly, regression analyses requested in relation to a subsequent technology appraisal by the UK's NIH and Care Excellence appeared to suggest that no patient characteristics were prognostic of outcomes among these patients with metastatic MCC. As such, the sponsor concluded that there was no need to adjust for prognostic factors or to use alternative methods, such as conducting a matching-adjusted indirect comparison [60]. However, the NIH and Care Excellence review team raised concerns around drawing conclusions based on statistically nonsignificant results from these regression analyses as they could arise due to small patient numbers rather than the absence of a prognostic effect [60].

Despite the challenges noted above, the use of historical data for unadjusted comparisons with clinical trial data was accepted as the only solution to the lack of a comparator arm in JAVELIN Merkel 200 and the difficulty in conducting a dedicated RCT in such a rare condition. Ultimately, these real-world analyses were recognized by the EMA as supportive of the avelumab submission [56].

Using RWE to support a new indication

The PD-1 immune checkpoint inhibitor nivolumab was initially approved by the FDA in 2014 for second- or later-line treatment of unresectable or metastatic melanoma. Over the following years, the FDA approved nivolumab for several additional indications, including renal cell carcinoma and non-small-cell lung cancer. In August 2018, the FDA granted accelerated approval for nivolumab use in patients with small-cell lung cancer (SCLC) who had progressed after platinum-based chemotherapy and ≥1 other line of therapy, primarily on the basis of clinical outcomes from the SCLC cohort of the CheckMate 032 clinical trial [61]. Before this approval, patients with SCLC failing ≥2 therapies typically received SoC chemotherapy. As CheckMate 032 did not include a SoC comparator arm, a population-adjusted indirect comparison analysis was performed to provide data on the effectiveness of nivolumab (with or without ipilimumab) versus SoC treatment approaches (i.e., non-I-O regimens) for patients treated with two prior lines of chemotherapy or chemoradiotherapy (i.e., third-line) for SCLC [62,63].

For this analysis, two comparator cohorts were constructed from a US-based real-world database that matched the inclusion/exclusion criteria of CheckMate 032. One cohort included patients receiving a third-line therapy who had not received an I-O agent in any line (n = 78), while the other cohort included patients receiving a third-line therapy that was not an I-O agent, but who had received I-O therapy in a previous line (n = 92). From CheckMate 032, individual patient data were extracted only from patients with two prior lines of therapy and who received third-line therapy with nivolumab alone (n = 78) or nivolumab plus ipilimumab (n = 43) [63]. In the main analysis, a regression-based indirect comparison was performed using a Cox regression model for nivolumab (with or without ipilimumab) and modeling OS using individual patient data from CheckMate 032. This model was used to predict survival outcomes for nivolumab (with or without ipilimumab) that would have been observed in the real-world database for comparison with outcomes for patients receiving SoC treatments. In addition, a matching-adjusted indirect comparison was performed as a sensitivity analysis, using a propensity score function.

Several methodological and data-related challenges were associated with this analysis. For example, sample sizes for each cohort were relatively small, resulting in substantial uncertainty in relation to the OS curves where numbers at risk were very small at later time points. In addition, the analysis methodology involved adjusting models for potential prognostic factors, which were identified via a targeted literature review; however, of the factors identified, only age, sex, race, smoking status, disease stage, platinum sensitivity and ECOG-PS were reported in both the CheckMate 032 and real-world cohorts, and thus could be considered for inclusion. Moreover, to prevent overfitting the multivariate models given the small sample sizes, the final model was adjusted for only four factors: sex, disease stage, platinum sensitivity and ECOG-PS. As such, there was a level of uncertainty regarding the potential influence of any unknown or unmeasured prognostic factors on survival; for example, information was not available on the presence of liver or brain metastases, or on prior surgery or radiotherapy. Even those factors included in the final model were reported in the real-world cohort with varying frequency; for example, while all

patients had information on sex and more than 95% had information on platinum sensitivity, a third of patients in the real-world database had no reported ECOG-PS.

Despite these challenges, the methods used for this analysis were considered the best attempt to account for between-study differences given the difficulty in evaluating comparative efficacy on the basis of a single-arm trial and in the absence of an RCT. Moreover, data from this analysis supported the clinical trial data from CheckMate 032 used to secure the new indication approval of nivolumab as a third-line treatment for metastatic SCLC. Of note, in a more recent Phase III clinical trial, nivolumab monotherapy did not provide a survival benefit over chemotherapy (topotecan or amrubicin) for patients with SCLC who progressed after first-line platinum-based chemotherapy, although the safety profile strongly favored nivolumab [64]. However, current guidelines for second- or later-line treatment of SCLC in the USA still include nivolumab ± ipilimumab (based on the CheckMate 032 data) and have also recently been expanded to include pembrolizumab [65], suggesting continued confidence in using PD-1 immune checkpoint inhibitors in later lines of SCLC therapy.

Using RWE in support of a proposed indication expansion across geographies

By late 2017, data from the randomized, double-blind, Phase III ATTRACTION-2 clinical trial had demonstrated significant clinical benefit of nivolumab over placebo for heavily pretreated Asian patients with advanced or metastatic gastric or gastroesophageal junction cancer (GC/GEJC) [66], leading to regulatory approval in Japan [67]. At the same time, data from the Phase I/II CheckMate 032 trial had indicated clinical activity of nivolumab monotherapy as third- or later-line therapy in patients with GC/GEJC or esophageal cancer from Europe and the USA [68]. While the CheckMate 032 results suggested similar efficacy for nivolumab in Western patients with GC/GEJC, there remained a need to bridge the placebo-controlled clinical trial data in Asian patients to a Western population. On this basis, a retrospective, observational study was conducted to evaluate baseline characteristics, survival outcomes and duration of therapy in US real-world SoC cohorts matched to patients with GC/GEJC who received ≥2 prior lines of therapy in the ATTRACTION-2 placebo arm or the CheckMate 032 nivolumab monotherapy arm [69].

In order to match patients from a US real-world database to the ATTRACTION-2 and CheckMate 032 arms, patients were identified who met inclusion/exclusion criteria similar to those used for ATTRACTION-2 and CheckMate 032. This was followed by frequency matching to align baseline characteristics in the real-world cohorts with the trial arms, with a focus on characteristics identified as significantly associated with OS in univariate analyses [69]. Figure 1 shows a schematic of the inclusion/exclusion criteria alignment and frequency-matching processes that resulted in the matched real-world cohorts used for the subsequent comparisons [69].

In addition to relatively small sample sizes, the main challenge for this comparison of RWD with data from ATTRACTION-2 and CheckMate 032 was related to the population-matching process. First, the initial step of this process had to be based on a relatively limited set of trial-specific inclusion/exclusion criteria. Moreover, while the subsequent frequency-matching process was successful in aligning the populations with respect to most patient characteristics, there were some noteworthy differences. For example, compared with patients in the ATTRACTION-2 placebo arm, patients in the matched real-world cohort had a higher median age (66 vs 61 years), a higher proportion had a primary tumor in the gastroesophageal junction (23 vs 7%) and a lower proportion had received ≥3 prior therapies (44 vs 82%) [69]. Similarly, compared with patients in the CheckMate 032 nivolumab arm, patients in the matched real-world cohort had a higher median age (64 vs 58.5 years) and a lower proportion had received ≥3 prior therapies (40 vs 57%). Univariate analyses assessing the influence of factors on OS indicated that only ECOG-PS (0 vs 1), disease stage (stage IV vs other stages) and site of primary tumor (GC vs GEJC) significantly impacted OS [69]. This suggested that the only imbalance likely to influence the comparisons would be the lower proportion with a primary tumor in the gastroesophageal junction in the real-world cohort matched to the ATTRACTION-2 placebo cohort. However, based on the relatively small real-world samples in this study, it is possible that differences in age and the number of prior therapies did influence survival outcomes, despite the lack of a statistically significant association with OS in the univariate analyses. Moreover, patient medical histories for the real-world cohorts were often incomplete and may have been inaccurate (e.g., due to misclassification and incomplete data entry), further challenging the veracity of this matching process.

While considering the limitations of the frequency-matching process, the comparisons performed were considered at the time the only viable method for bridging the Asian clinical trial data to a Western population in the absence of an RCT in Western patients. Although available RWE was included in the regulatory-marketing applications, it

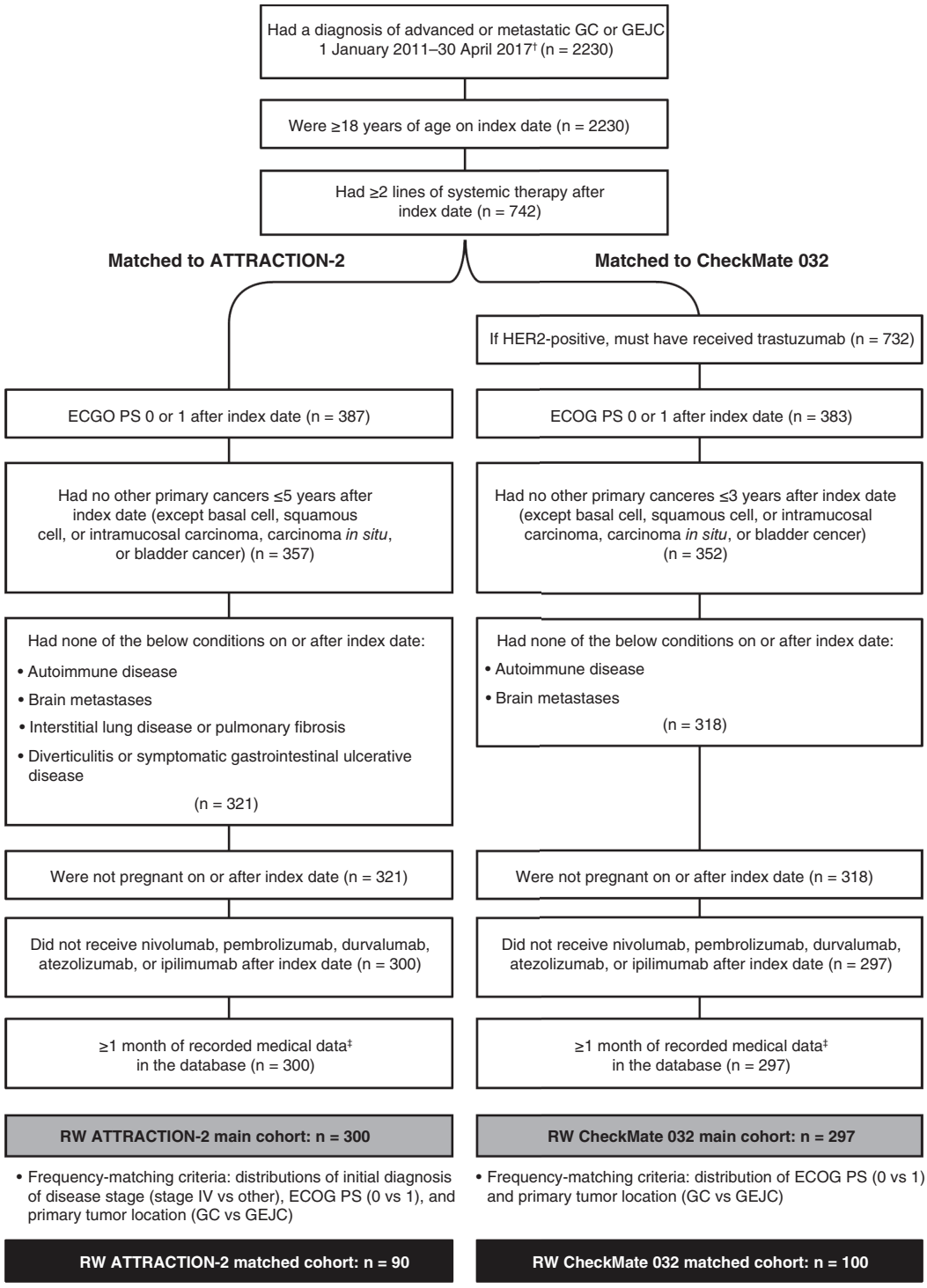

Figure 1. Inclusion/exclusion criteria alignment and frequency matching for patients in US real-world standard of care cohorts matched to the ATTRACTION-2 placebo and CheckMate 032 nivolumab monotherapy arms.

†Excluded patients who were enrolled in clinical trials.

‡Defined as data from outpatient physician office visits, nonfacility visits, laboratory visits, treatment/procedure visits or medication administration.

ECOG PS: Eastern Cooperative Oncology Group performance status; GC: Gastric cancer; GEJC: Gastroesophageal junction cancer; RW: Real world.

was determined that these data did not provide sufficient proof of generalizability of effect across Asian and Western populations.

Using RWE as postmarketing support for an indication approval

For the past 20 years, adjuvant IFN-α-based immunotherapy has been a mainstay of treatment for patients with high-risk resected melanoma [70]. Building on this success, ipilimumab was approved by the FDA in 2015 as adjuvant therapy for fully resected stage III melanoma [71], and nivolumab was approved by both the FDA and the European Commission in 2017/2018 as adjuvant therapy for resected melanoma with involvement of lymph nodes or metastatic disease [72,73]. These regulatory approvals were based on results from Phase III RCTs showing that adjuvant ipilimumab and nivolumab prolonged recurrence-free survival when used within 12 months of resection [74,75]. However, there remained at the time a need to assess the benefits of adjuvant I-O therapy on OS among patients with melanoma who progressed to the advanced stages of the disease. As such, a retrospective, longitudinal, EHR-based study was conducted to evaluate real-life survival outcomes among patients with advanced melanoma in relation to whether they had received adjuvant therapy and the type of adjuvant therapy received [76,77].

For the study, data were extracted from a US real-world EHR-derived database for adult patients with advanced cutaneous melanoma (unresectable, stage III–IV) who had ≥2 nonconsecutive clinical encounters between January 2011 and June 2018. This resulted in a final eligible cohort of 1497 patients, of whom 182 had received adjuvant therapy [77]. Fifty-five had received adjuvant therapy with 'new' I-O agents, primarily ipilimumab, nivolumab or pembrolizumab; 65 had received adjuvant therapy with 'older' I-O agents, primarily IFN-α-2b or peg-IFN-α-2b; and 62 had received adjuvant therapy with non-I-O agents, primarily fluorouracil, vemurafenib, carboplatin/tamoxifen and bendamustine. The remaining 1315 patients had not received adjuvant therapy. Comparisons were made between new I-O agents, older I-O agents and non-I-O agents versus no adjuvant therapy, as well as between both new and older I-O agents versus non-I-O agents; outcome measures were OS and progression-free survival.

This study faced several methodological and data-related challenges. For example, despite starting with a pool of nearly 1500 patients, only 182 had received adjuvant therapy, leading to relatively small sample sizes for the 'adjuvant therapy' subgroups and weakening statistical power of some of the analyses. The small sample sizes may have also contributed to the observed lack of a statistically significant influence of adjuvant therapy on progression-free survival. An additional contributing factor to this observation may have been the frequent need to use proxies for disease progression under real-world conditions (e.g., the date of 'progression' may in fact be a proxy, such as the date of starting subsequent therapy). Furthermore, the real-world database did not contain complete patient histories and treatment-related details, so there may have been imbalances between the compared subgroups that could have impacted respective survival outcomes.

Despite these challenges, by showing that newer adjuvant I-O therapy was associated with significantly improved long-term survival versus both no adjuvant therapy or non-I-O adjuvant therapy, this research informed the clinical understanding of the risk:benefit assessment of adjuvant I-O therapies among patients progressing to advanced melanoma and assisted in regulatory decision-making.

Conclusion

In the burgeoning field of I-O, there is a need for rapid regulatory assessment of new and existing treatments in order to expedite patient access in the context of addressing unmet medical need. While these assessments are driven primarily by clinical trial data, there is an increasing role for RWE. However, generation of RWD for regulatory submissions faces challenges, many of which are common across all new drugs and biologics, but some of which are unique to I-O agents.

Building on insights from the reviewed literature and the four case studies described above, we see several key ongoing challenges for the use of RWE in the I-O regulatory process, including small sample sizes, missing/incomplete data, real-world end point definition and availability, and undefined requirements for 'regulatory-grade' RWE. In our cases, the primary methodological and data-related challenges were small sample sizes and missing/incomplete data, with both associated with other limitations typical for RWE studies, such as the potential for unknown population imbalances, confounding factors, misclassification issues and selection bias to influence population-matching methods and outcomes. These challenges represent noteworthy limitations as they increase the level of uncertainty regarding the statistical analyses performed and outcomes observed, and raise questions regarding the generalizability of the findings. The challenge of small sample sizes, while common across many indications, may become more

prominent for I-O therapies as they are increasingly being studied in rare cancers, with inherently smaller patient populations. Similarly, although missing/incomplete data are also relatively ubiquitous in real-world studies, this limitation, and the associated issues with population matching, may pose a somewhat unique challenge for the I-O field, since I-O agents can be associated with durable survival and evaluation of long-term survival benefits may therefore need to be achieved via real-world research rather than lengthy clinical trials. Importantly, observations from our cases could inform on the key methodological and data-related areas of focus for initiatives aimed at enhancing the role for RWE in the regulatory assessment of I-O therapy. For example, investigating the potential for innovative real-world study designs and end points and novel methodological and/or statistical approaches aimed at limiting the impact of small sample sizes or missing/incomplete data would be of great benefit.

In terms of policy-related challenges, the field would benefit from a greater consensus on what constitutes 'regulatory-grade' RWE. While recent framework documents and guidance have started the process of defining 'regulatory-grade' RWD [1,34], there is a need for greater communication between regulators and industry on reaching benchmarks for acceptable RWE. Agreement between parties on 'approved' methodology, such as acceptable data harmonization techniques, analytical approaches and end points, would be particularly useful for optimizing the utility of RWE in regulatory submissions. In addition, there may also be a need for agreement on how best to ensure integrity and transparency regarding RWD generation. Recommendations by the Real-World Evidence Transparency Initiative Partnership, including the encouragement of real-world study registration and upfront provision of study protocols and statistical analysis plans, are an initial step in the right direction [78]. Endorsement of such processes and procedures by regulatory bodies would, of course, be essential to establishing these processes as best practice.

Thus, while methodological, data-related and policy-related challenges persist, RWE has had, and will continue to have, an important role in regulatory approvals of I-O agents. Our cases highlight some of these challenges and inform on key areas of focus for future research to establish a greater role for RWE. Moreover, the potential lessons learned from the cases described in this article may be applicable to the role of RWE in regulatory assessments of other therapeutic classes or in nononcology indications. Ultimately, increased alignment between regulators and clinical sponsors will be essential for achieving a defined application of RWE in informing development and regulatory processes in the expanding I-O field.

Future perspective

With enhanced communication and greater alignment between regulators and industry, the hope is that a clear RWE roadmap will emerge in the upcoming years facilitating routine generation of 'regulatory-grade' RWD to support the approval of new I-O therapies. In addition, although certain challenges such as small sample sizes and missing/incomplete data will persist, ongoing and future research into novel study designs, end points, methodologies and statistical approaches should advance our ability to lessen the impact of these limitations on robust RWD generation. Moreover, while the expectation is that data from RCTs will continue to be critical for regulatory appraisal of new I-O agents, continued research on the capacity for duplicating clinical trial results using RWD may inspire an even greater role for RWE in the regulatory process, particularly in therapy areas where RCTs are not feasible or unethical.

Author contributions

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Executive summary

Background
- Although data from randomized controlled trials are the standard for new drug evaluations, there are situations where conducting a robust clinical trial is not practicable or where the time required to conduct a clinical trial might be seen as an unacceptable delay to patients accessing novel treatments.
- Under these circumstances, there is increasing recognition that real-world evidence (RWE) of effectiveness and safety has an integral role in supplementing and supporting new drug applications.
- Assessing effectiveness and safety in real-world populations may be particularly important when clinical trial results lead to dramatic shifts in standard of care for broad groups of patients, as has been seen recently with the emergence of immuno-oncology (I-O) therapies for numerous cancer types.

RWE & regulatory assessments of new therapies
- Although the role of RWE in the regulatory process has traditionally been to supplement existing approvals (e.g., for indication expansion), there are several examples where RWE was used to support or supplement new drug approvals, mostly in the rare disease and/or oncology settings.
- However, generation of RWE for regulatory decision-making is subject to various operational, methodological and data-related challenges.
- There is increasing recognition among regulators of the need to address these challenges, and various initiatives are underway in Europe and the USA with the aim of developing novel real-world study designs and end points and improving and standardizing methods and statistical approaches.

Impact of RWE on regulatory policy
- Regulators in Europe and the USA have begun to establish frameworks and industry guidance on the use of RWE in regulatory submissions.
- Nevertheless, there remains a lack of clarity on what constitutes 'regulatory-grade' real-world data (RWD) and an associated need for increased communication between regulatory bodies and those submitting data packages, particularly regarding exactly what is required from the RWD for the related evidence to inform their decisions.

RWE & the regulatory assessment of I-O agents
- Immunotherapy for cancer is a rapidly expanding therapeutic area; several immune checkpoint inhibitors are already standard of care for multiple tumor types and many more I-O agents are in the development pipeline.
- In this fast-changing therapeutic landscape, there is a need to rapidly assess new I-O agents, which may in some circumstances be better served using RWE, rather than data from randomized controlled trials.
- Nevertheless, generation of RWD on I-O treatments is affected by many of the same challenges as experienced with non-I-O treatment classes.
- Case studies are presented in which RWE on I-O treatments and outcomes were used to support regulatory submissions, each highlighting some of the associated methodological and data-related challenges.

Conclusion
- The reviewed literature and presented case studies highlight several key ongoing challenges for the use of RWE in the I-O regulatory process, including small sample sizes, missing/incomplete data, real-world end point definition and availability, and undefined requirements for 'regulatory-grade' RWE.
- Solutions to these challenges revolve around greater alignment between regulators and industry. Through enhanced communication, agreement can be reached on topics such as 'approved' methodologies and end points, integrity and transparency processes during RWE generation, and definitions of 'regulatory-grade' RWE.

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- **Recent draft white paper on how to improve integrity and transparency in relation to real-world studies and associated RWD/RWE.**

Panel discussion: real-world data in clinical trials

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What will you learn?

- How outcomes research is shaping the design of clinical trials
- The future of RWD use alongside clinical trials
- How RWD can help payers with the value of diagnostics
- How COVID-19 has changed treatment habits

Who may this interest?

- Researchers and clinicians working in the multidisciplinary field of RWD and clinical trials
- Regulatory bodies
- Oncology investors

Panelists:

William Audeh
Chief Medical Officer
Agendia (Los Angeles, USA)

William Audeh, MD, MS is a medical oncologist specializing in breast cancer, with nearly 30 years of experience as a clinician and clinical researcher at the Cedars-Sinai Cancer Center in Los Angeles. Prior to joining Agendia, and in addition to his clinical practice, he served as the former Director of the Cedars-Sinai Cancer Center and Medical Director of the Wasserman Breast Cancer Risk Reduction Program.

Dr Audeh also served as Director of the Medical Oncology Training Program for Breast Surgery and Surgical Oncology Fellowships at Cedars-Sinai, and is Associate Clinical Professor of Medicine at the UCLA David Geffen School of Medicine. Dr Audeh has been Principal Investigator on a wide variety of national and international clinical and translational trials, and has authored numerous publications in the field of breast cancer, cancer genomics, and targeted cancer therapy.

Dr Audeh received his medical degree from the University of Iowa and an M.S. Degree in Genetics from the University of Minnesota. He went on to complete his residency in Internal Medicine as well as a fellowship in Medical Oncology at Stanford University Medical Center. He is board certified on internal medicine and medical oncology, and is a member of the American Society of Clinical Oncology and American Association of Cancer Research.

Jacob Adashek
Internal medicine resident
University of South Florida and H. Lee Moffitt Cancer Center & Research Institute (FL, USA)

Dr Adashek is a second-year internal medicine resident at the University of South Florida and H. Lee Moffitt Cancer Center & Research Institute. He is interested in oncology and clinical trial design. He has presented research at various international meetings and has contributed to work published in top medical journals worldwide. Dr Adashek's work focuses mainly on targeted and immunotherapeutics and novel combinations in n-of-1 trial designs.

Gorana Capkun
Head RWE Enablement
Novartis Oncology (Basel, Switzerland)

Gorana Capkun is heading Enablement of Real World Evidence at Novartis Oncology. She is a published leader within the healthcare industry, with a particular interest in identifying novel ways of creating evidence, defining value, developing and bringing healthcare solutions to improve the lives of patients. Gorana is a strong believer in the power of dialogue between all partners in finding sustainable solutions to healthcare challenges.

She successfully combines her knowledge in statistics, health economics, real world evidence and market access with her experience from all phases of drug development across multiple disease areas to estimate product value and optimize access for patients.

Gorana holds a PhD in Applied Statistics from Swiss Federal Institute of Technology in Lausanne, Switzerland and is Associate professor or research methodology at University of Split, Croatia.

Sreeram Ramagopalan
Global Head for Real World Evidence for Market Access
Roche (Basel, Switzerland)

Sreeram (Ram) Ramagopalan is the Global Head for Real World Evidence for Market Access at Roche. Dr Ramagopalan's team strategically plans and executes real world research studies to obtain and maintain access for Roche medicines. Dr Ramagopalan holds a PhD in Epidemiology from the University of Oxford, as well as an MSc in Epidemiology from the London School of Hygiene and Tropical Medicine. He is an international expert in real world evidence with over 270 peer reviewed publications.

Allison Betof Warner
Assistant Attending Physician on the Melanoma Service
Memorial Sloan Kettering Cancer Center (NY, USA)

Allison Betof Warner, MD, PhD is an Assistant Attending Physician on the Melanoma Service at Memorial Sloan Kettering Cancer Center. Dr Betof graduated magna cum laude from Cornell University and went on to graduate with her MD/PhD from the Medical Scientist Training Program at Duke University. She completed her PhD under the supervision of Drs Mark Dewhirst and Lee Jones, studying tumor angiogenesis and effects of vascular normalization on chemotherapeutic efficacy. Dr Betof went on to Internal Medicine residency at Massachusetts General Hospital then Medical Oncology Fellowship at Memorial Sloan Kettering Cancer Center. Her research explores how modulations in tumor microenvironment affect tumor immunobiology immunotherapy.

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