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How RWE Was Used For Opdivo, Abecma & Orencia Approvals

by Neena Brizmohun

Bristol Myers Squibb's use of real-world evidence in US and EU marketing applications for three of its products shows how population bridging, external controls and comparative effectiveness might be employed.

The use of real-world evidence (RWE) is increasingly being used to support regulatory decisions when it comes to the approval of new medicines or extended indications. Knowing when to use RWE in regulatory submissions is key, according to Bristol Myers Squibb's Rob Kalesnik-Orszulak, who shared his company's experiences with using RWE in marketing applications for three BMS products – Opdivo (nivolumab), Abecma (idecabtagene vicleucel/ide-cel) and Orencia (abatacept).

There are various ways in which RWE might be used in a regulatory context from a sponsor perspective, noted Kalesnik-Orszulak, who is director, regulatory innovation lead for RWE & data science, at *BMS*.

"We oftentimes think about these uses in respect to the type of different regulatory objectives or submissions where RWE might be used, such as new product approvals, new indications, new dosing, the addition of new efficacy or safety data into the label, as well as post-marketing requirements."

"However, the weight of the RWE in respect to the rest of the evidence in the submission might vary from one application to the next," Kalesnik-Orszulak said. "More fundamentally, the specific way in which RWE is used in each of these submissions might also vary quite considerably."

Kalesnik-Orszulak was speaking at the 2021 TOPRA (The Organisation for Professionals in Regulatory Affairs) annual symposium, where he gave a presentation entitled: RWE in Regulatory Decision-Making: Sponsor Learnings & Experiences*.

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It is important for companies "to go one layer deeper and think about how, in a more specific way, RWE might be used to help support" their regulatory objectives, he said, adding that the use of RWE was "not always appropriate."

The BMS executive discussed examples of how RWE could be used for regulatory purposes, covering external controls; population bridging; comparative effectiveness; long- term effectiveness; endpoint establishment; and safety monitoring. He expanded on the various points as follows:

RWE V RWD

Real-world data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Real-world evidence (RWE) is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Source: US FDA

- External control – where RWE is used as an external benchmark for context or as a formal comparator to a single-arm trial or indirect comparison. "Here is where real-world observational data might serve as the control arm to a single-arm clinical trial," Kalesnik-Orszulak said. "These have been used in certain select situations to help support new product approvals and new indications. Typically, this is when a randomized clinical trial may not be feasible or may be very challenging to conduct in a particular setting."

- Population bridging – where RWE is used to help bridge the applicability of clinical trial results to a particular sub-population that may not have been well represented in that original trial. "For instance, perhaps the pivotal study was run in one region of the world and you're trying to bridge to another or perhaps the clinical study used one particular standard of care but in a certain country where you're trying to get approval, they actually use a different standard of care. Here, RWE can be used… to help bridge into those different populations or regions and help support approval or label updates."

- Comparative effectiveness – where RWE is used to compare the benefit between treatments. "[This is] where the comparison of the investigational agent to the comparator or control is conducted entirely within the real-world data. So here, usually your agent is something that's being prescribed off-label to be able to get that data or perhaps you're running a pragmatic trial."

- Long-term effectiveness – using RWE to measure longer-term outcomes than that studied in a clinical trial.

- Endpoint establishment – using RWE to support the establishment of a new surrogate endpoint being used in a clinical trial.

- Safety monitoring – using RWE for pharmacovigilance.

Kalesnik-Orszulak stressed that the examples he discussed were non-exhaustive and that there were other potentials uses of RWE.

A Good Fit?

As for determining whether RWE might be a "good fit" for a regulatory submission, Kalesnik-Orszulak said there were important factors that companies should consider that "tend to circle around the particular research question or evidence gap that you're actually trying to address with the real-world data."

For example, RWE regulatory approaches may be most appropriate where randomized controlled trials are not feasible, ethical, or the best way to address the gap, or where there is a high magnitude of treatment effect, he said.

> *"[Companies need to be] teasing out why… RWE might be an appropriate way to address [their] research question or evidence gap."– Kalesnik-Orszulak, BMS*

Companies should also consider "whether the endpoint of interest that you're trying to assess is one that's objective, and actually captured routinely in clinical care."

In addition, it is important that fit-for-use real-world data (RWD) is available for analysis or can be generated.

Basically, companies need to be "teasing out why… RWE might be an appropriate way to address [their] research question or evidence gap."

Real-Life Cases

Kalesnik-Orszulak discussed how BMS used RWE to support marketing applications for Opdivo, Abecma, and Orencia.

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Opdivo & Population Bridging

For Opdivo, BMS used RWE via population bridging to help support a filing to use the drug for a new indication in the US – for treating patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

The company's pivotal, randomized clinical trial – ATTRACTION-3 (ATT- 3) – had evaluated Opdivo versus standard-of-care chemotherapy for ESCC but the study had been conducted predominantly in Asia, Kalesnik-Orszulak explained.

Only around 4% of the randomized population had been Western patients. "So, there was some uncertainty [over] whether the results would be actually applicable to the US population, which is a western population."

The company decided to use RWE from the US "to present [the] relevance of ATT-3 data to medical practice and outcomes of patients treated in the US."

In addition to the use of other types of data, including the medical literature, two real-world observational studies were conducted to evaluate the outcomes of patients receiving standard-of-care chemotherapy in the US. One of these real-world observational studies used electronic health care records and the other used linked registry and claims data.

"These studies essentially showed that the clinical practice and survival outcomes in the US for standard-of-care chemotherapy were similar or, at least, not significantly different than those outcomes seen for the standard of care in Asia, as observed in the clinical study, or in the medical literature," Kalesnik-Orszulak said.

The inclusion of these data strengthened the filing package that was submitted to the US Food and Drug Administration and contributed to the ultimate marketing approval of Opdivo for ESCC in the US in June 2020, the BMS executive said. ATTRACTION-3 had shown "a very large differential effect for Opdivo versus standard of care chemotherapy, and the RWE showed that "this could be applicable to the US patient population."

The RWE also highlighted the high unmet need for more effective therapies to improve survival outcomes in second-line (2L) ESCC. Opdivo was the first immuno-oncology therapy approved for 2L ESCC in the US, Kalesnik-Orszulak noted.

Abecma & External Control

For Abecma, BMS used RWE as an external control in relapsed and refractory multiple myeloma (RRMM) to help secure pan-EU conditional marketing authorization for the one-time, CAR T-cell therapy for RRMM patients in a late-line setting – ie patients who have received at least three prior therapies.

The pivotal clinical trial of Abecma was KarMMa (MM-001), a single-arm study with the primary endpoint of overall response rate (ORR) – KarMMa enrolled 140 patients, of whom 128 patients were treated with Abecma.

"As a single-arm trial, the primary evidence gap here was the lack of control data," Kalesnik-Orszulak explained.

BMS's decision to opt for a single-arm trial approach followed discussions between the company and the European Medicines Agency early on during the development of Abecma, which had been accepted onto the EMA's PRIME (priority medicines) scheme.

Conducting a randomized clinical trial of the product in the given indication would have been a challenge. This was due to "the varied treatment landscape with a high number of different [approved] products in this very late-line, high unmet medical need setting," Kalesnik-Orszulak said, noting also that a "very high magnitude effect" had been observed with the early clinical data for Abecma."

BMS decided to pursue a single-arm approach, with a systemic literature review (SLR) plan to provide some context around the expected outcomes of patients who were receiving the varied standard of care in the very late line setting involved.

However, the EMA had concerns around the company's plan to provide a literature review summary but not an external control containing patient level data.

It "recommended that beyond just a systemic literature review, which will only contain aggregate patient data, BMS should consider the use of an external control where you can have patient-level data to help better characterize and quantify the magnitude of benefit in this particular situation," Kalesnik-Orszulak said.

As per scientific advice from the EMA, the company conducted a global, non-interventional, retrospective study – NDS-MM-003 – to generate RWE in patients with RRMM. NDS-MM-003 was designed to generate an external comparison arm for study MM-001 including patient-level data from 190 eligible RRMM subjects treated with currently available therapies.

BMS also had discussions with the agency "for alignment of the protocol advice."

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Several different types of RWD from multiple data sources were used for NDS-MM-003. Electronic health care records, registry data and also clinical site data were all harmonized into a common data model for the study, Kalesnik-Orszulak said.

As explained in the EMA's *public assessment report* for Abecma, a propensity score methodology was used "to ensure that real-world subjects were comparable to the ide-cel cohort. "

The assessment report continues: "The selected cohort of 190 real-world subjects for the eligible RRMM cohort provided an adequate match for only about 80 subjects in the Abecma cohort. As a result, the primary analysis method had to be changed. Trimmed stabilised IPTW [inverse probability of treatment weights] was used as the primary analysis method for the effectiveness endpoints and are the data presented throughout this report. Matched-pair and untrimmed stabilised IPTW analyses were utilised as supporting analyses."

The adjusted indirect comparisons to the NDS-MM-003 study demonstrated a clinically relevant and statistically significant benefit for Abecma across all pre-defined efficacy endpoints, with an ORR of 69.4% for the Abecma enrolled population versus 32% for the real-world eligible cohort.

The EMA was satisfied that the comparison showed clinically relevant and statistically significant benefit for Abecma across all pre-defined efficacy endpoints, Kalesnik-Orszulak said. It said that the efficacy results compared favorably to those in the matched real-world historical cohort as well as those reported in the literature.

The EMA was also very clear about some of the key limitations of this comparison, the BMS executive noted. These limiting factors included: a long time period (up to 60 days from the index date) allowed for collection of baseline data; overlapping recruitment periods of the real-world study and the MM-001 study at the same study centers; and a large proportion of missing data (up to 30%) for some included co-variates and several co-variates excluded from the propensity score model due to >30% missing data.

Despite the limitations, the EMA considered that the results indicated that Abecma was associated with responses well above the current standard of care. The treatment was approved by the European Commission in August, becoming the first cell therapy authorized in the EU for treating fifth-line multiple myeloma.

Orencia & Comparative Effectiveness

As for Orencia, BMS used RWE in the supplemental biologics license application (sBLA) that it filed in the US to use the drug in a new indication – for the prevention of acute graft versus host disease (aGvHD).

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In the filing, the company used RWE "as comparative effectiveness," Kalesnik-Orszulak said.

The sBLA was based on results of the Phase II ABA2 trial and a registry trial based on RWE.

The ABA2 trial assessed Orencia added to standard GvHD prophylactic regimen in patients with heme malignancies receiving stem cell transplant from unrelated-HLA (human leukocyte antigen)-matched or mismatched donor.

ABA2 showed that treatment with Orencia resulted in a significant reduction in severe aGvHD and associated morbidity without an increase in disease relapse, Kalesnik-Orszulak said. "The findings of the real-world analysis were consistent with those of ABA2."

On 15 December, BMS said that Orencia had won US marketing authorization for preventing aGvHD, becoming the "first FDA-approved therapy to help prevent this serious complication that impacts between 30-70% of hematopoietic stem cell transplant recipients." (Also see "*Keeping Track: Immunology Drives US FDA Action, With Approvals For AZ/Amgen's Tezspire, Argenx's Vyvgart, And New JAK Uses*" - Pink Sheet, 17 Dec, 2021.)

Final Thoughts

Wrapping up his presentation, Kalesnik-Orszulak gave industry delegates at the TOPRA symposium some principles to consider when using RWE.

"It's really important to be clear why RWE is being used," he said. "What is the research question/data gap and why is RWE the most appropriate way to address it?

> ***"It's very important to basically engage regulators up front and get alignment before you conduct your study." – Kalesnik-Orszulak, BMS***

It was also "important to be honest" about the real-world data sources. "Do they capture the endpoints and important covariates needed, and with sufficient completeness?"

Employ rigorous real-world study methods, Kalesnik-Orszulak said, adding that this "comes down to trying to reduce bias." Also, a key aspect here is pre-specification, "so if you're trying to use RWE in any sort of significant way, it's very important to basically engage regulators up front and get alignment before you conduct your study."

Finally, the BMS executive told delegates to be realistic about the use of RWE. This is "certainly a very exciting area that holds a lot of promise," he said. Nevertheless, RWE "is not appropriate for all situations... and it's important to think long and hard about whether or not the situation that maybe you're considering is a good fit for RWE or is it not?

** The 2021 TOPRA annual symposium took place virtually on 22-24 September.*