How HTAs approach single arm trial evidence in oncology

ACHIEVING EARLY ACCESS IN ONCOLOGY WITH NON-COMPARATIVE DATA

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Introduction

An increasing number of oncology drug candidates are gaining regulatory approval based on non-comparative phase II trials. While some may bring potentially transformative patient benefits in areas of high unmet need, they also present a sizeable challenge for payers and HTA agencies as they seek to gauge the value such therapies bring based on limited data. As a result, although accelerated regulatory approval can be achieved, securing reimbursed access may prove to be more difficult.

Market Access Transformation engages with industry experts online through our Rapid Payer Response (RPR) plaform, which can gather semi-quantitative responses in as little as 5 days. We conducted a retrospective analysis of over 410 payer engagements in last 4 years and found that not only are there multiple drivers and barriers to achieving access based on non-comparative data, but they often vary from one market to another, adding complexity to early access strategy preparation.

The Market Access Transformation team recently met with current and former HTA and payer experts from France, Italy, and the UK to further discuss early access in oncology based on non-comparative evidence, along with the associated challenges and opportunities for drug developers.

In the first of a three-part series of white papers, we take a close look at how HTA agencies and payers manage access to oncology medicines without comparative data.

HTA ACCEPTANCE VARIES BETWEEN COUNTRIES

The way in which HTA agencies approach single arm trials varies across the different countries. In France, for example, it is difficult to obtain access and favourable pricing outcomes if the evidence is from a single arm trial, particularly as it can be hard to show additional medical benefit vs. standard of care. In France, the main focus is on demonstrating potential for a significant magnitude of effect, in which case there is a degree of flexibility in areas of high unmet need. As the French HTA expert, an ex-member of the Transparency Commission in France, comments “The access is quite difficult for an early single arm trial, usually HAS denies an additional medical benefit. There have been some exceptions to the rule… but if you don’t have a huge effect, like a complete response with the CAR T, you might be challenged. It’s not about the unmet need, more the clinical benefit, it’s more whether or not the transparency committee could acknowledge and gamble on a novel survival benefit... so, I would say that their flexibility depends on the benefit you are making compared to standard of care. The bigger the benefit, the higher the likelihood that HAS would accept a single arm trial compared to traditional randomized research”.

On the other hand in Italy, AIFA will consider single arm trial data in specific circumstances, but will focus on the reasons this approach was adopted and what benefit can be derived. A former national and regional payer in Italy, explains “The drivers are mainly… the stability and robustness of the single arm trial evidence and the reason why the manufacturer decided to design the trial with a single arm.” Nevertheless, even when the rationale for a single arm trial is accepted and the evidence seen as robust, the process is more complicated than where there is comparative data from head to head trials. The situation can be further complicated by AIFA’s innovation algorithm, which uses three criteria to evaluate a new drug. While the unmet need and incremental patient benefit can still be shown even with single arm data, the level and quality of evidence is harder to show – although not impossible – as former Italian payer comments, “Evaluation is based on three main criteria. One is the importance of the disease and the unmet needs. The second one is incremental clinical benefit for the patient. The third area is the level of quality of the evidence. It is a bit more relaxed for all drugs and indications where it is more difficult [to have a] double blinded trial”.

COMPARATIVE ANALYSIS IS KEY FOR NICE APPRAISAL, BUT THE CANCER DRUGS FUND OFFERS A ROUTE TO DEAL WITH UNCERTAINTY IN ENGLAND

All oncology medicines in England are assessed by NICE and, in most cases, these require comparative evidence to perform robust health economic analysis for the appraisal. As a clinical lead for the Cancer Drugs Fund in England and former member and chair of the NICE technology appraisal committee, explains “There has to be this robust assessment of clinical effectiveness, but the biggest uncertainty often is that the indirect comparison has to be done with some form of control group.” In the absence of these comparative, control data, the achievable price will be limited and the manufacturer has to make a decision on what route to take. Former chair of the NICE technology appraisal committee remarks “The decision [for] manufacturers is [to choose between] what’s called a routine commissioning decision, where the drug is approved and it is in practice in effect until it’s superseded? Or do they want to go into what we call a Cancer Drugs Fund, some would call it an early access arrangement… whilst data matures and therefore uncertainty can be reduced.”

The Cancer Drugs Fund allows for oncology drugs with limited clinical data, such as that collected through a single arm trial, to be accessed by patients and funded by the NHS while additional data is being collected and analyzed. After a period of access, usually two to three years, NICE will reassess the data and decide whether approval should be granted for wider access. This has become a standard way for companies to alleviate the risks of single arm data in the UK, as the UK HTA expert comments “The Cancer Drug Fund has become a very clear route for those types of drugs that come for licensing from the regulator with small phase two data.”

HTA AGENCIES HAVE ADOPTED A MORE FLEXIBLE APPROACH IN SOME CASES

Despite the preference for comparative data, HTA agencies in France, Italy and the UK have recognized the need for flexibility when reviewing certain new drugs. Where the unmet need is high and the opportunity for a head to head trial is limited, single arm data can be used to assess the product and some form of access is often granted. This was the case with the CAR-T therapies that have recently been approved in Europe for the treatment of two different blood cancers - Acute Lymphoblastic Leukaemia (ALL) and Diffuse Large B-cell Lymphoma (DLBCL). Due to the nature of the products and the high unmet medical need within these two indications, both were approved based on early phase, single arm data. Despite this, both CAR-Ts were given access at an unprecedented speed post regulatory approval based on single arm trial data. The French authorities, felt that the magnitude of effect observed in phase II trials and the indirect comparisons provided by Novartis and Gilead showed potential additional benefit and this warranted a positive decision. In the UK, the Cancer Drugs Fund provided a balanced solution to ensure access to these innovative therapies, while collecting sufficient data to complete the standard NICE assessment at a later date.

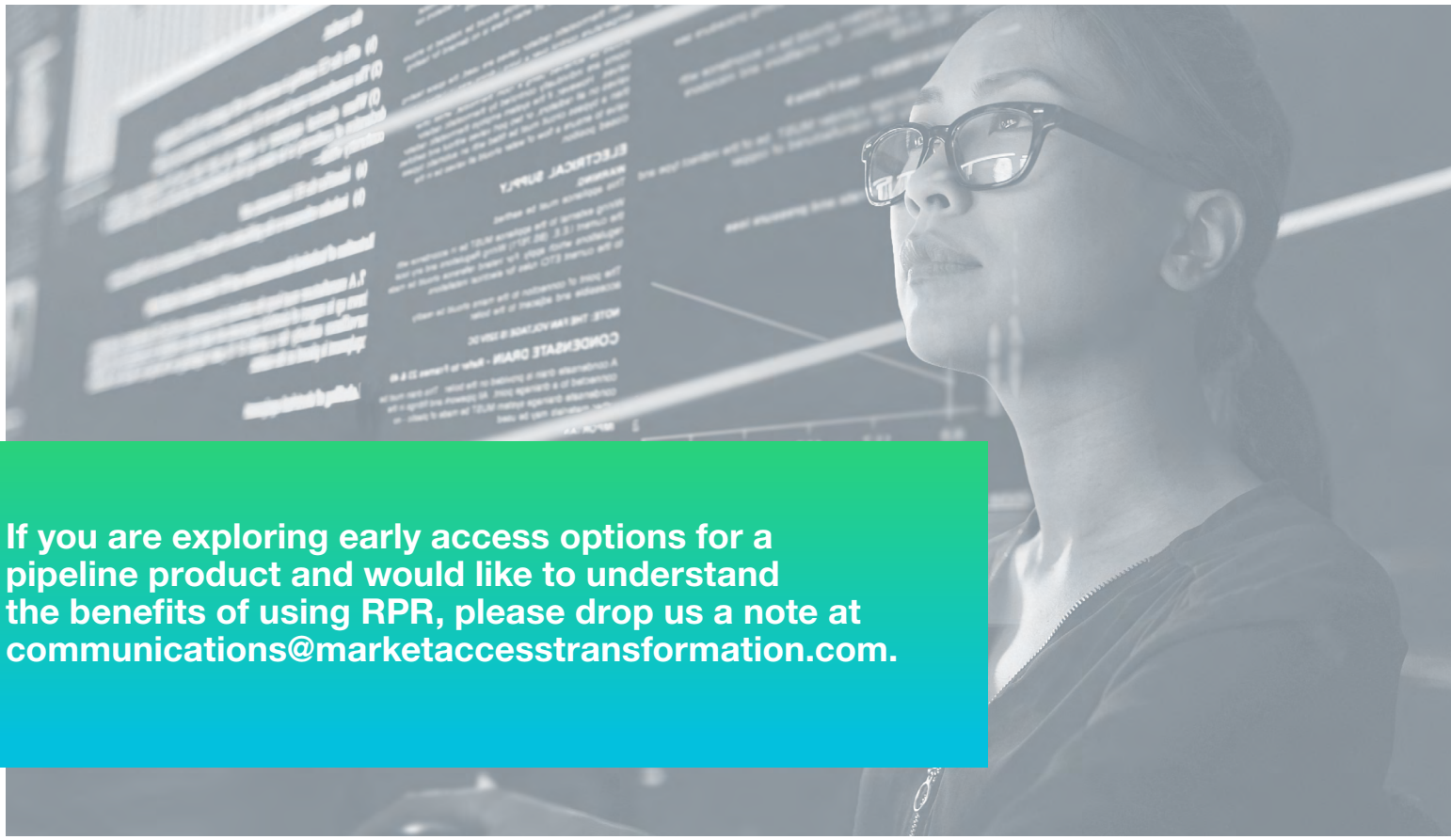
HTA AGENCIES MUST BE PRAGMATIC, BUT REALISTIC MANUFACTURER EXPECTATIONS ALSO ADVISED

As shown by the recent experience with the CAR-Ts, HTA agencies do recognize the need to be flexible in the face of high unmet need. The Italian HTA expert highlights that, while AIFA prefers to have comparative data in order to perform the HTA and grant full access, "AIFA established that in special cases…the comparative evaluation …can be less important when specific results justify the use of a single arm trial." Indeed, it is still possible to obtain the much coveted "innovative status" in Italy even without comparative data, further demonstrating how HTA agencies are adopting a more pragmatic approach to the raft of novel innovative therapies emerging from the pipeline. As the Italian HTA expert comments "Good examples are the two CAR-Ts, of course many orphan drugs are developed with a single arm trial because the number of patients is very limited. The most interesting examples are in non-small cell lung cancer because crizotinib has been developed with a single arm trial and it was reported at the time the same for brigatinib in same line of therapy."

In the UK, early and honest interaction with NICE about the potential limitations of the data will help smooth the process, as the UK HTA expert explains "Be truly honest about the strengths but critically, also the weaknesses of the data that you're coming with. Recognize them head on, because by doing that you will get NICE on your side."

In contrast, in France, there are fewer situations where exceptions will be made that need to be taken into consideration, as the French HTA expert comments "Many new biologics and small molecules will be challenged, and then the access is either zero if it's an IV product with no funding on top of DRG or it's a very tough price negotiations. It's why I think at the stage of POC, when the companies are willing to launch their product in France, they should consider whether they are in the [situation of having a] questionable likelihood of success with a single arm or just having to wait until they have more mature data and more knowledge in order to apply to the French market."

While head to head comparative data is still the much lauded standard, in certain circumstances such as high unmet need, small patient population or few, if any comparators, less mature, single arm data is no longer a barrier but a hurdle that is being made easier to overcome.



If you are exploring early access options for a pipeline product and would like to understand the benefits of using RPR, please drop us a note at communications@marketaccesstransformation.com.

About Market Access Transformation (MAT)

Founded by industry veterans, MAT specializes in developing cutting edge technologies that enable the healthcare community to gather and exchange insight that assess the real-world potential of their products. MAT offers an online, information exchange platform, Rapid Payer Response™ (RPR), that is revolutionizing the way to global payer insights.

About Rapid Payer Response™ (RPR)

Rapid Payer Response™ (RPR) is an agile, on-demand platform that allows you to conduct faster, higher quality, more insightful research via direct payer engagement. Through our global payer network, it is possible to gather more accurate, robust feedback by probing further and asking deeper questions at any time, ensuring you always have the exact answers you need in a fraction of the time and cost of a traditional payer research project.

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