Moving beyond a reliance on overall survival evidence to enable timely patient access to new and emerging cancer medicines

Judith Hinton Andrew, *Rock Composite 22 (4ft)*
Artwork from The Creative Center, a nonprofit organisation dedicated to bringing creative arts to people living with and beyond cancer and other chronic illnesses.

Advances in science and treatment have enabled improved outcomes for people living with cancer

Despite successive scientific and medical advances, cancer – in its many forms – persists as one of the most devastating and challenging public health issues worldwide. In Europe alone, there were 1.9 million deaths in 2018 due to cancer.[1]

This accounted for one in four deaths and was the second leading cause of mortality following cardiovascular disease.[2]

Cancer remains a devastating public health challenge

Driven by this health challenge, scientific research has focused on gaining an increasingly detailed understanding of this disease area, in order to develop safe and effective treatments for patients as rapidly as possible.

As such, scientific progress in the field of cancer has accelerated rapidly

There is now a significantly advanced understanding of the immunologic underpinnings of the disease, genomics and molecular characterisation of tumours.[3] This progress has led to innovation in both the development of new treatments and clinical research.

An unprecedented level of choice exists today

Pharmacological treatment of cancer has expanded from chemotherapy and hormonal agents to the use of targeted treatments and the recent introduction of immunotherapies.[4-6] Another important treatment milestone was passed with the authorisation of the first cell and gene therapies in 2018,[7] representing a new chapter in personalised cancer care. This has resulted in an increase in the number of therapeutic options available across many cancers,[8-12] with effective new treatments allowing longer-term therapy and improved tolerability.[13]

This evolution in the cancer treatment landscape has generated an unprecedented level of choice and clinical promise, with new therapies, and combinations thereof, enabling treatment paradigms to continuously advance.

Cancer-related deaths are decreasing

Over the last decade, whilst there has been an increase in the number of new cancer cases due to population growth and population aging, cancer-related deaths have reduced by 12% across Europe.[14] While continued improvements in earlier detection and diagnosis have played their part in reducing mortality, so too has the availability of therapeutic advances. For example, the 5-year survival rate for multiple myeloma has increased 4-fold faster than other cancers over the period 1990-2011 (60% in multiple myeloma vs. 15% in all cancers).[15] This improvement has been attributed to the availability of a series of transformational classes of medicines that have become established as the standard of care for patients.[12,16]

For many years, overall survival has been the gold standard outcome in cancer clinical trials

OS has traditionally been used by regulatory authorities for benefit-risk assessment[17,18]

The choice of outcomes to measure the incremental clinical benefit of a new medicine is critical to the design of clinical trials and these serve different purposes dependent on the stage of development.[19]

> In clinical trials conducted for the purposes of regulatory authorisation, study outcomes commonly evaluate whether the new treatment provides a clinical benefit, such as an improvement in overall survival (OS), a delay in disease progression, maintaining or improving quality of life, or a reduction in cancer-related symptoms.[17,18]

For many years, OS has been accepted as the gold standard outcome of clinical benefit, being objective, measurable and of principal clinical and patient relevance.[20,21] A convincingly demonstrated improvement in OS versus the current standard of care has been regarded as the clearest indication that an intervention provides clinical benefit.[22] This outcome has traditionally been used by regulatory agencies such as the European Medicines Agency (EMA) as the basis of informing their benefit-risk assessment[a].[17]

[a] The European Medicines Agency's (EMA) opinions are based on balancing the desired effects or 'benefits' of a medicine against its undesired effects or 'risks'. The EMA can recommend the authorisation of a medicine whose benefits are judged to be greater than its risks. In contrast, a medicine whose risks outweigh its benefits cannot be recommended for marketing.

Overall survival as the primary measure of assessing benefit is not always feasible or practical[25]

Cancer is not a single disease

Through advances in research, we now better understand that cancer is not a single disease, but a collection of diseases, each with unique characteristics, clinical features and therapeutic modalities for treatment. These fundamental differences inform the expectations of clinical outcomes for researchers, clinicians and patients when considering the role of a new treatment being introduced into a specific phase of the disease, where the intention of treatment can be curative, life-extending or end-of-life palliation.

In some situations, OS is key

Therefore, there are circumstances where OS is of primary relevance and readily quantifiable in a clinical trial, such as in advanced disease, or cancers where there are limited effective treatment options. For example, pancreatic cancer is a particularly aggressive and life-threatening malignancy. Despite intensive research efforts over past decades, the prognosis of advanced pancreatic cancer currently remains dismal with an average life expectancy of 6-12 months (5-year survival rate of 7%) due to limited therapeutic advances.[23,24] In this situation, OS is the key, relevant outcome for assessing treatment benefit and measurable in an appropriate timeframe of a clinical trial.[23,24]

In other situations, OS may not be feasible or practical

In contrast, advances in science and treatment have given rise to new and increasing situations where the demonstration of a clinically meaningful or comparative OS benefit is not available at the time of regulatory or reimbursement assessment. The drivers for this include; the increased number of more effective and better tolerated treatments compared to traditional approaches (i.e. chemotherapy), the ability to combine synergistic therapies, moving treatments earlier in the disease continuum with the aim of achieving cure, and the emergence of novel treatments through advanced research that demonstrate a step-change in clinical benefit for populations that were previously unserved. As such, the demonstration of an OS benefit may not be feasible or practical in a clinical trial.[25] ▶

This challenge with regards to OS evidence can be categorised into two main situations:

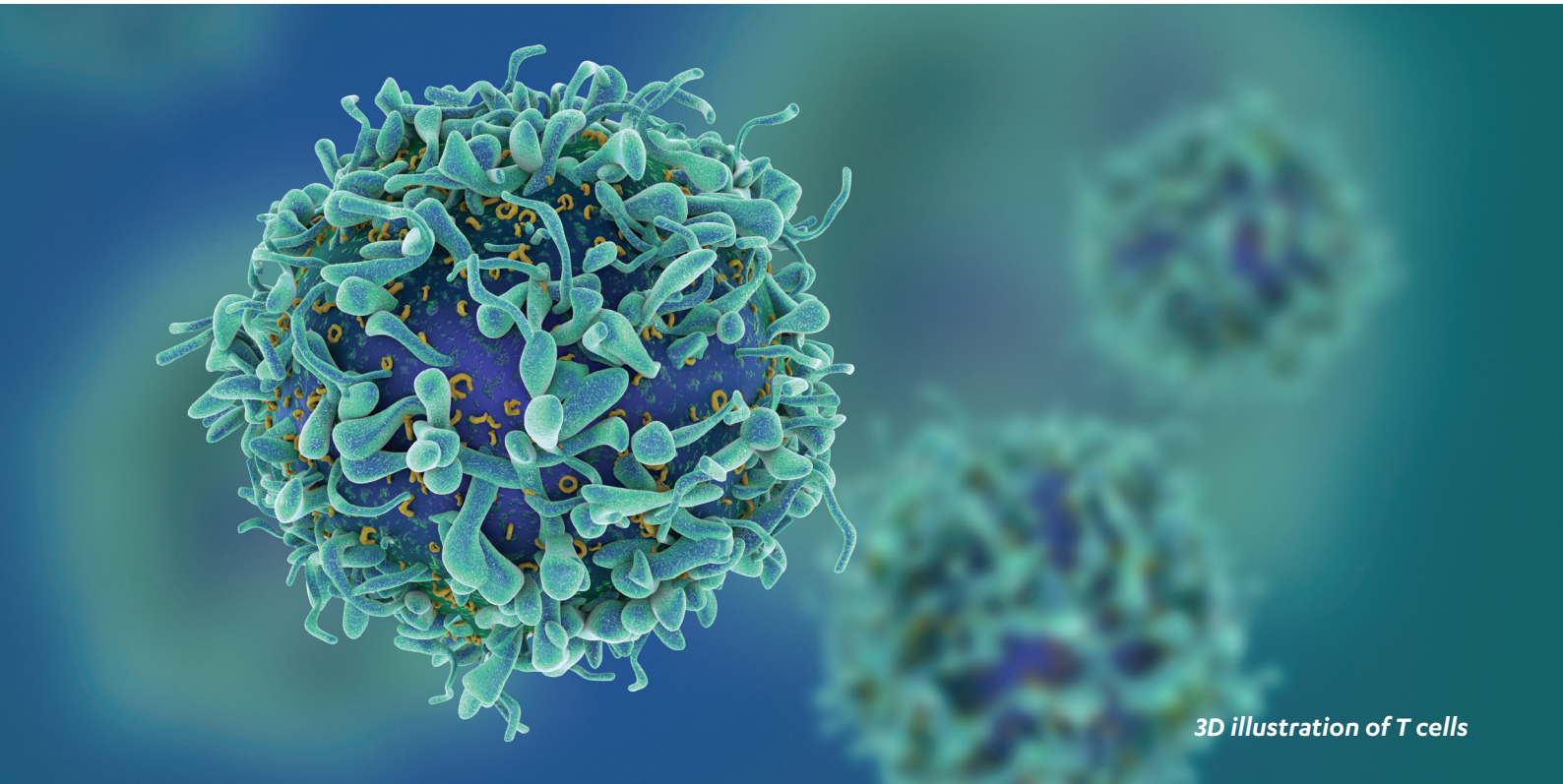
1. Mature OS evidence will not be available at the time of regulatory or reimbursement assessment, or for several years thereafter:

- **In settings where highly effective treatments have the potential to substantially extend life.** For example, in a disease setting such as newly diagnosed multiple myeloma, treatment with lenalidomide and dexamethasone has demonstrated an extension of median OS to almost 5 years (representing an additional year of OS compared to the previous standard of care).[26] The addition of a further treatment to this known effective combination is anticipated to extend OS even further,[27] and likely beyond a reasonable timeframe of a clinical trial.
- **In settings where there is an availability of additional effective therapies that can be given following disease progression on the initial treatment.**[28] In such cases, an early assessment of OS may erroneously suggest no benefit for the treatment of interest, as patients continue to receive further treatments which also extend life. For example, in advanced breast cancer, it has become increasingly difficult to detect an OS benefit for new treatments because of the growing number of active treatments and associated combinations.[29]
- **In certain cancers, or disease settings, the progression of the disease may take many years to assess OS.**[18,30] For example, in early disease settings where the intention of a new cancer treatment is to cure patients, will require many years of follow-up.[30]

2. Single-arm trial[b] and the absence of comparative OS evidence due to ethical or feasibility challenges of conducting a randomised controlled trial:[c]

- When a new treatment demonstrates evidence representing a step-change in treatment benefit (e.g. early evidence of an unprecedented objective response rate)[d] in an area of high unmet need, with no alternative treatment options. Clinical equipoise is lost, making it unethical to conduct a randomised controlled trial (RCT) against an inferior alternative.[31]
- In rare cancers, or patient populations with a specific biomarker, conducting an RCT may not be feasible due to the low numbers of eligible patients.[32]

[b] Single-arm trial: A study type, where every individual enrolled will be treated with the same experimental therapy.
[c] Randomised controlled trial (RCT): A study in which people are allocated at random to receive one of several clinical interventions. RCTs seek to measure and compare the outcomes between interventions.
[d] Objective response rate: Proportion of patients with a reduction in tumour size by a pre-determined amount.



3D illustration of T cells

Regulatory methods have evolved to enable timely authorisation of new or promising cancer treatments

T cell lymphocyte with receptors to kill cancer cell

Alternative or intermediate endpoints considered for benefit-risk assessment

In recognition of these challenges and evolving science, regulatory agencies have revised their recommendations on study endpoints with the aim of enabling more rapid development of, and access to, new or promising cancer medicines.

These include greater acceptance of the use of alternative endpoints such as prolongation of progression-free survival (PFS), or disease-free survival (DFS)[e] and achieving minimal residual disease (MRD)[f] negativity alongside conventional assessments of cancer-related symptoms and patient functioning.[17,33] Intermediate endpoints, such as PFS or DFS are now broadly considered relevant for the purposes of primary benefit-risk assessment of many cancer treatments.[17] In these instances, OS is also assessed alongside these intermediate endpoints to ensure that there is no indication of a long-term adverse impact.[17]

Alternative regulatory pathways e.g. accelerated approval

Additionally, in an attempt to stimulate and accelerate development of treatments in areas of high unmet need, regulatory agencies can exercise flexibility in determining the evidence required for authorisation - particularly when the potential therapeutic benefit may justify a greater degree of uncertainty in the benefit-risk assessment. Alternative regulatory pathways have been in operation for many years in Europe (e.g. conditional marketing authorisation)[g] and in the United States (e.g. accelerated approval) with the intention of enabling faster patient access. Between 2006-2018, 19 cancer medicines were granted conditional marketing authorisation.[34-36]

OS decreasingly used as a primary endpoint in registrational studies

There has been a clear paradigm shift in how regulatory agencies assess cancer medicines and the degree of OS evidence required for authorisation. This is most vividly illustrated in EMA regulatory authorisations over the last three years, where OS was not commonly (<10%) used as a primary endpoint in registrational studies.[37] Of these cancer medicines, approximately 2 in 3 approvals were in the absence of data demonstrating statistically significant OS benefit versus the trial comparator. Moreover, half of the evidence packages for the purposes of primary registration were comprised of single-arm trials.[37]

Whilst regulatory agencies have exercised flexibility in the evidence requirements for regulatory authorisation the development of cancer medicines remains challenging. The probability of success of new cancer medicines is lower than non-cancer medicines across all development phases,[38] particularly during Phase III, which is also the costliest phase.[39]

[e] Disease-free survival: Period between randomisation in a trial and the recurrence of a tumour or death.
[f] Minimal residual disease: Evidence for the presence of residual cancer cells, even when so few cancer cells are present that they cannot be found by routine methods.
[g] Conditional marketing authorisation: The approval of a medicine that addresses unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefit outweighs its risk and the developer should provide comprehensive clinical data in the future.

Benefits to patients from cancer medicines and their timely approval are put at risk by additional hurdles to access

Despite the paradigm shift in how regulatory agencies have adapted their traditional approval procedures and evidence expectations to accelerate the approval of innovative cancer medicines, reimbursement of new cancer medicines has become increasingly methodologically complex, differentiated and inflexible to adapt to the novel treatments in development.

Measuring value and inter-country variation in HTA methods

Common to all national Health Technology Assessment (HTA)[h] agency processes, is an attempt to assign a measure of value to the medicine under evaluation, and the level of certainty associated with this measure. Typically, this is in the form of an assessment of relative effectiveness, calculation of a cost-effectiveness (value for money) ratio, or a combination of decision-making criteria. There also exists country-specific preferences or requirements related to HTA methods and processes based on national healthcare system needs, which introduce inter-country variation in HTA recommendations for a given medicine.[40]

HTA preference for OS evidence

Irrespective of approach, the assignment of value is based on individual HTA agency expectations towards the quality, maturity and relevance of the clinical evidence package available at the time of initial evaluation. OS evidence remains a preferred criterion for many national HTA agencies.[25] This can result in perceived uncertainty regarding the value of the treatment in the situations where OS evidence is not available at the time of evaluation.[41,42] Certainty in the overall benefit-risk can in some instances be achieved through more time. However, there are also instances where time or other factors will not enable meaningful or interpretable information on the OS benefit.

Patients face delays where OS is not available

The consequences are that patients in immediate need of intervention may face delays or barriers in accessing innovative cancer medicines because of perceived uncertainty regarding the therapeutic benefit.[42]

This can result in extended negotiations or divergence in value assessment between local agencies and manufacturers impacting reimbursement and pricing decisions:

Time to patient access: The average time between regulatory authorisation and patient access to a new cancer treatment is approximately 14 months in Europe. There is also significant country-by-county variation in time to reimbursement across Europe, with a difference of 2.5 years between the fastest and slowest European country (Denmark average time of 67 days, Estonia average time is 988 days).[43]

Barrier to patient access: In some European countries, HTA agencies may also impose restrictions based on defined criteria that can limit patient access to treatment, or alternatively, specifically recommend against reimbursement for a given treatment. For example, in England and Wales, nearly 50% of medicines reviewed in 2018 by the National Institute of Health and Care Excellence were 'recommended with restrictions' and 10% were 'not recommended' for national health system funding.[44]

HTA requirements counteract regulatory strategies to expedite access

In summary, HTA agency requirements regarding evidence and data certainty remain inflexible, resulting in delays or barriers to patient access. This counteracts the attempts of regulatory agencies to facilitate faster patient access and transform clinical research into routine clinical practice and may lead to avoidable cancer-related mortality and morbidity.

[h] Health technology assessment: A process for the systematic evaluation of the social, economic, organisational and ethical issues of a health intervention or health technology (e.g. a medicine). The main purpose of conducting an assessment is to inform policy decision making.

The HIV example: What can we learn from other disease areas that faced a similar challenge?

Melinda, *Total Tranquility*, HIV patient

Advances in care over the last 30 years have helped transform human immunodeficiency virus (HIV) from a fatal disease into a chronic, manageable condition for many people.[45] Innovations in treatment and access have been at the core of this progress. However, for an initial period following the first identification of the disease in 1983,[46] society faced a similar challenge in terms of timely patient access to innovation.

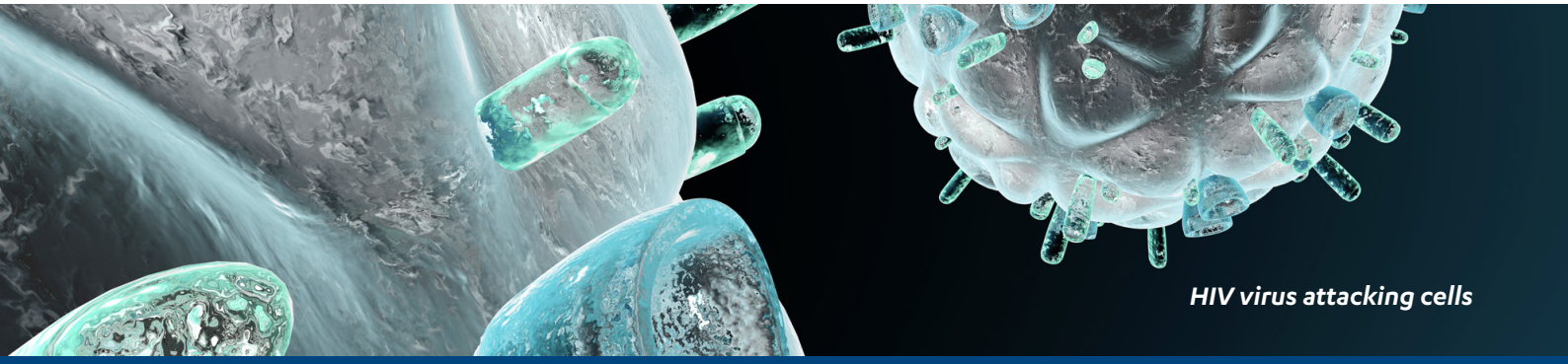
Clinical trials during early HIV drug development were designed as large-scale studies, using progression to acquired immunodeficiency syndrome (AIDS) and OS as the outcomes. At the time, these represented the only outcomes of relevance, and despite a poor prognosis, clinical trials still required several years to initiate and complete, resulting in delays in defining the optimal therapeutic treatment, which had a detrimental impact on the widening AIDS epidemic. This led to a concerted effort to accelerate new drug development through identification of surrogate endpoints.[47]

During the late 1990s, advancing science enabled the advent of highly sensitive molecular tools for the detection of biomarkers of the disease,[47] in parallel to the approval of a generation of antiretroviral treatments that represented a step-change in outcomes (termed, highly active antiretroviral therapy).[48] Scientific research enabled the validation of these biomarkers, when used in conjunction with treatment, to be predictive of disease progression and OS.[49] The findings were so consistent across trials and populations, that this enabled a paradigm shift for new drug approvals based on alternative outcomes (i.e. viral suppression).[50] This has translated into an accelerated drug development and approval process for new HIV treatments.[47]

This was achieved through mutual stakeholder agreement for the research and validation of surrogate endpoints for new treatments to enable regulatory authorisation and subsequent HTA for timely patient access. Today, there are currently six classes of medicines, and over 30 medicines in total, approved for the treatment of HIV.[51] As a consequence of this development and subsequent array of accessible highly effective medicines, HIV is considered a chronic disease where individuals can live long and full lives.

Whilst recognising the underlying differences between these disease areas, increased awareness of the evidence challenges in cancer (as similarly observed in the HIV example) is needed to evoke action in the identification, assessment and implementation of solutions to enable timely patient access to new and emerging cancer treatments.

[h] Surrogate endpoint: An endpoint that is not itself a direct measure of patient survival but is predictive of survival and should capture the impact of treatment in the same way as a 'true' endpoint; can provide a more rapid and specific indication of the efficacy of a therapy.



HIV virus attacking cells

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