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Tumour Review

Overcoming the barriers to treatment of rare cancer patients in the era of precision oncology: A call to action☆

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ABSTRACT

Rare cancers account for a quarter of cancer diagnoses in Europe yet clinical research, diagnosis, treatment access, and survival outcomes lag significantly behind common cancers. Despite the potential of precision oncology, the consistent implementation of comprehensive genomic profiling in routine clinical practice and robust evidence-generation remains a challenge in this population, compounded by regulatory hurdles and a lack of investment in drug development. A concerted effort across all stakeholders is required to optimise diagnostics, including access to molecular profiling, to expedite clinical trials and treatment access, and to gather high-quality data, including patient-reported outcomes, in rare cancers. Some initiatives are already showing promise including the establishment of national expert reference centres and European Reference Networks such as EURACAN. However, further collaboration is required to speed up the diagnostic trajectory so that rare cancer patients present with less late-stage disease, and to facilitate clinical trials leading to wider access to precision oncology drugs shown to be safe and effective. In the context of so many hurdles (diagnosis, treatment, research, development and regulatory), there is an even greater role for patient and clinical trial organisations and funders to help fill the aforementioned gaps. Innovative solutions are urgently required to address the high unmet medical need for patients with rare cancers.

☆ Based on the multi-stakeholder Cancer Drug Development Forum (CDDF) Workshop 'Innovation and Access in Rare Cancers' (September 23–24, 2024), sharing insights from industry leaders, regulators, academics, patient groups and non-commercial organisations.

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Introduction

Rare cancers account for about 25 % of cancer diagnoses and have significantly worse overall survival than more common cancers [1]. Patients with rare cancers often present with late-stage disease due to prolonged diagnostic pathways and lack of treatment options, often finding themselves in very frightening, isolating and hopeless situations [2,3]. Genomics has reshaped the cancer treatment landscape, from a one-size-fits-all approach in a given histology (i.e. tumour type or location) to the molecular era of cancer classification which has led to the development of histology-independent therapies targeting genetic or molecular features of a tumour [4]. The development of targeted biomarker-based drugs has been extremely dynamic, with the number of pan-tumour therapies receiving Food and Drug Administration (FDA) approval expected to increase from currently 9 to ~30 by 2028 (based on current Phase 2 and Phase 3 studies; David Thomas, personal communication). Thus, the new paradigm of precision oncology has much potential for the treatment of rare cancers and cancers of unknown primary (CUP) [4].

However, there is a global consensus that drug development and access for patients with rare cancers is not as efficient as for more common tumours, with often limited interest from the pharmaceutical industry, translational and clinical research significantly lagging, and major disparities in research funding. Together, these factors have led to a lack of available treatments, creating a high unmet medical need (HUMN), with rare cancers representing arguably the greatest inequality in cancer research and treatment [5]. Revisiting the fundamentals of clinical research for rare cancers is long overdue in order to ensure that anyone with a rare cancer can promptly access precision oncology therapies.

Challenges with drug development and availability in rare cancers

Academic perspective: classification and patient access

Personalised cancer treatment using a biomarker-based approach is often associated with significantly better outcomes than treatment with classical unspecific cytotoxic chemotherapies [6–9]. Therefore, molecular subtyping of cancer is a necessary tool complementing histological and immunological characterisations. However, this has also resulted in nosological fragmentation: frequent cancers fragmented into a series of rare cancers and a myriad of even rarer oncological entities, and similarly 'classical' rare tumors which have ultra-rare molecular subtypes leading to the requirement of novel molecular-targeted clinical trial designs.

Although the trend in cancer drug development is moving towards histo-agnostic approaches (e.g. the positive Phase 1–2 basket study of larotrectinib in NTRK fusion-positive tumours [10]), a differential response to the same targeted therapy can still be observed across different histotypes (e.g. the first basket study of non-melanoma BRAF V600 mutation-positive cancers treated with a BRAF inhibitor) [11,12]. Therefore, there is no one-size-fits-all across histologies, with histological subtypes remaining important determinants of response to be integrated in the drug development strategy. Moving forward, the definitions of a given rare cancer and of 'histology-independent response' will be critical for trial design and reporting, and also for reimbursement of molecular testing and treatment.

The Australian Molecular Screening & Therapeutics (MoST) study for patients with rare cancers found an extension of survival from 15 to 23 months and an improved quality of life (QoL) with therapies for which there is at least prospective Phase 2 or higher evidence for clinical benefit [13]. By creating a framework to mainstream therapies shown to be highly effective and safe such as those approved in some jurisdictions (e.g. EU or US) across a pan-tumour setting, we could expedite the routine global access to treatments for rare cancer patients. As a community, given the historical lack of success to manage these patients, we must exploit the paradigm shift from precision oncology to re-engineer the classical methodological approach to drug development for more efficient access in rare cancers.

Industry perspective: regulatory hurdles, and the need for harmonisation and incentivisation in Europe

The orphan drug (OD) regulatory framework in the EU began in 2000, 17 years after the US OD act first issued in 1983, and unlike that of the US, it includes the need to justify a 'significant benefit' over existing therapies to avoid 'me too' drugs that demonstrate no satisfactory treatment available for patients with improved efficacy or better safety or tolerability. Unsurprisingly, in the EU vs the US, there are fewer OD approvals (244 vs 1,235, respectively in September 2024) and fewer OD designations authorised (2,871 vs 6,889, respectively in September 2024). The low rate of OD approvals vs OD designations of 8.5 % in the EU (vs 18 % in the US) shows that the majority of projects do not materialise, failing either at non-clinical or clinical trial stage or due to failure to raise capital for further development. Nonetheless, the EU regulation has provided an effective framework establishing a stable regulatory environment for rare diseases which must be maintained in the ongoing revision of the current European Pharmaceutical Regulation (expected entry into force in 2027–2028). Among the potential issues raised by industry are the following planned updates to this legislation:

(1) Introduction of the concept of HUMN giving higher priority or special status with respect to patients deemed to have just an 'unmet medical need', thereby alienating substantial numbers of patients by discriminating those whose disease is not classified as HUMN.
(2) Shortening of the OD designation validity from an unlimited timeframe to 7 years (renewable) thereby impacting the ability of small biotechs/startups/academia to raise capital or sell their asset to bigger companies due to having less time to develop their innovative OD.
(3) Decreasing the marketing exclusivity and data protection timeframes, thereby decreasing the appetite of some companies to develop more than one indication for the same asset.

Other significant Europe-specific regulatory challenges for industry include the implementation of early patient access programmes in Europe (i.e. Compassionate Use [CU] per the European Medicines Agency [EMA], or Expanded Access [EA] per the FDA), notably a complete lack of harmonisation around terminology and procedures (Table 1). There is a fundamental need to harmonise and bring consistency to the terminology as a first step to facilitate CU access across Europe. The use of different terms for CU programmes across individual countries adds further hurdles to industry trying to navigate the CU regulatory landscape in order to offer treatments to patients. Industry is also requesting an overall greater harmonisation and clarity of the legislations, and more transparency on CU procedures across Europe as part of the revision of the Pharmaceutical Legislation. The stable EU regulatory environment for OD development must be preserved, with more specific regulatory pathways to expedite early access in particular to single patients with rare cancers and also through streamlined and harmonised CU cohort programmes.

In addition to the challenging EMA legislation for CU, there is also insufficient awareness of available CU programmes, with no central European CU registry/database (in contrast, EA programmes in the US can be found on clinicaltrials.gov). Some European Health Authorities (HA) mandate publishing their CU programmes (e.g. UK and France), and some companies publish their CU programmes on their websites. However, there is a great need for transparency about CU availability across Europe to address this access inequality and an important role for patient advocacy groups to bridge this knowledge gap.

Table 1
Regulatory challenges with implementing CU per the EMA regulations in Europe (industry perspective*).

Issue	Consequences
EMA Regulation is high-level and vague, it differentiates between the CU Cohort versus individual CU single patient requests: either in different regulations (like EMA: cohorts in the Regulation, single patients in the Directive) or not clarified at the national level at all.	Confusion and lack of clarity; country by country interpretation and respective diverse regulation, with MS implementing different kinds of regulations at the national level making it very difficult to navigate.
Menu of different terminologies for CU (i.e. early/pre-approval access) by different stakeholders, and non-existent for post-trial access.	Regulations use different terms causing much confusion for different actors in the healthcare system as to whether referring simply to 'early/pre-approval access' for desperate patients.
Each EU MS has its own distinct requirements for labelling the unauthorised medicines (i.e. what is written on the pack and in what language [English vs local language]), and also for CU Cohort vs individual CU use.	No harmonization! Tailored labels required from one country to another which is tedious and time consuming when setting up CU programmes. All the more trickier for single patient CU requiring case-by-case assessment and to be very reactive (i.e. prompt to provide the correct and appropriate label for these drugs per a specific country if not already prepared) versus as part of a CU programme/group cohort for which drug labels can be pre-prepared.
Free of charge versus paid CU: varies by country so again not a homogenous system – some countries mandate a price, some require a symbolic price, while others are optional or not regulated (mostly free of charge).	Not a regulatory challenge per se but linked to regulation – differences for patients depending on where patients live, can cause delays to access. E.g. France mandates having a price, even if not paid by the patients but rather the healthcare system, however this leads to price negotiation which delays the process of getting the drug to the patient.
Data collection in patient CU/early access programmes – lack of guidance, lack of consistency for what should be submitted to HTA, and not permitted in some countries.	No consistency, poor data quality, missed opportunities for data collection in rare and paediatric settings leading to a delay in approval, or even to no approval at all due to a lack of data.

CU, compassionate use; EMA, European Medicines Agency; MS, Member States.
* Based on an industry collaborative presentation at the workshop presented by Philipp Schlatter (Roche, Switzerland), on behalf of the other collaboration partners: Nina S. Heiss (Merck KGaA, Germany), Paul Lacante (BMS, Netherlands) and Patrick Meshaka (Novartis, France).

Furthermore, there is an increasing use of real-world data (RWD) extracted from CU programmes for HA submissions for market approval, particularly in rare diseases where evidence from randomised clinical trials is scarce. However, there is a significant lack of guidance, clarity and consistency across EU countries, with evidence gathering from CU programmes being altogether not permitted in some, or data considered differently by individual HAs (i.e. pivotal vs just supportive/supplemental data; Table 1). Although the primary intent of CU is patient access rather than data gathering, these inconsistencies are hindering evidence generation opportunities in rare cancers.

Finally, to address the challenges in research and development (R&D) for rare cancer treatments, there is an urgent need for EU governments to foster more investment into research including fundamental research in academia, to preserve industry incentives for R&D, and optimise the OD regulatory ecosystem. From the perspective of an investor contemplating funding the R&D of a promising therapeutic asset for a rare cancer, the target market will involve a much smaller patient population, automatically decreasing return on investment. The regulatory environment (e.g. stability, adaptability, expedited pathways), as well as market exclusivity and data protection laws (e.g. intellectual property) will also be major considerations for investors, particularly to mitigate the small target population. Industry must somehow convince investors that their capital will be recovered in the rare cancer space, especially in Europe with its more complex regulatory environment. Unsurprisingly, it is more difficult for small start-ups and biotech companies to raise capital in Europe versus the US. Therefore, solutions are needed to improve the financial incentives and rewards (e.g. government support, research grants) in order to create a positive ecosystem in which sponsors feel comfortable investing in risky R&D projects in Europe and elsewhere, including for rare cancer treatments.

Adolescents and young adults (AYA) with cancer: challenges and measures to improve access and knowledge

Cancer is the fourth cause of death in AYA globally [14]. Whilst cancer has no age limit, the current R&D landscape is such that there is a separation between adults and paediatrics ('the 18-year dogma'), with AYA patients having limited access to clinical trials [15]. While the number of adult trials has increased over the years, there have been no improvements in numbers of paediatric and transitional trials over the last decade, across all AYA cancers and all phases of drug development [15]. Moreover, there is a significant delay between the start of drug development in adult and paediatric populations (median ~6.5 years, up to 30 years). Only 13 % of drugs approved by the FDA for an oncology indication in adults (1997–2017) had started paediatric development at the time of initial approval [16]. Sponsorship also plays an important role in this crisis: only 5.2 % of industry-sponsored oncology trials are open to patients aged under 18 years, and only 31 % of transitional trials have industry sponsors/cosponsors [15,17]. Although academic sponsors are more prone to widen the age inclusion criteria, this remains insufficient for AYA.

Therefore, the separate paediatric and adult oncology drug development landscapes ultimately lead to delayed AYA access to efficient drugs approved in adults for diseases also common in AYA. This lag is also caused by issues with the current European Paediatric Regulation, such as the need to apply for a Paediatric Investigation Plan (PIP) with its associated complexities, and the problem of product-specific waiver based on adult disease, leading to no drug development in a paediatric disease having the same target as an adult disease [18,19]. Furthermore, in a recent survey of 124 AYA oncology professionals, only 35 % of respondents were aware of the FDA's guidance on the inclusion of 12–17 year old patients in adult early-phase trials [20]. Collectively, these hurdles ultimately result in the off-label use of new effective drugs approved in adult indications with limited evidence gathering for their use in AYA. In consequence, much useful information on AYA cancer treatments is not being collected, including data on drug efficacy, safety and tumour biology, but also which might inform subsequent drug development in AYA (e.g. drug mechanism of action and resistance). Further regulatory flexibility along with greater collaboration between paediatrics and medical oncologists are urgently needed to facilitate cancer drug development and access in AYA patients.

The European ACCELERATE platform is an international collaborative working to improve paediatric cancer drug design and regulation (https://www.accelerate-platform.org/). The international Fostering Age Inclusive Research (FAIR) group of ACCELERATE, set up in 2017 to reduce this inequality in access for AYA patients and abolish the 18-year dogma, advocates that early drug development be based not on the age of the patient but on mechanism of action. The FAIR group calls for the inclusion of adolescents into adult trials from early phases (Phase 1/2) as a rational, rapid and safe solution to the current HUMN in these patients, on the basis that there are no real barriers hindering joint adolescent/adult clinical trials from early drug development [18]. Notably, there is no increased risk for adolescents vs adults, based on comparison of paediatric and adult Phase 1 trials showing similar pharmacokinetics (PK), similar recommended dose and less acute toxicity for adolescents ≥12 years compared with adults [21]. Trials are the safest way for an adolescent with cancer to access new drugs when scientifically and medical justified, in an appropriate paediatric and/or AYA care

Table 2
Potential issues with comparative datasets.*

Potential weaknesses for interpretation of the datasets	• Use of historical controls/Absence of randomisation • Variability of the pre-treatment and background treatments • Variability of recruitment across cohorts in basket trials • Surrogate endpoints • Subjective assessments • Variability of response evaluation (interval, technique, RECIST or not) • Enrichment strategies may create an imbalance in other aspects – i.e. potentially miss capturing other heterogeneity factors such as demographics or micro-environment, thereby raising doubts regarding the value of the surrogacy for decision-making
Limits of retrospective RWD	Often poor quality of retrospective datasets from external control arms (including data from routine practice): • Suggested methods uncertain (e.g. underlying assumptions often cannot be tested) • Data required for effect estimation (confounders, endpoints) often not available in the required quantity and quality (especially not from routine practice data sources) • Not only has the SoC changed over the years from historical datasets, but there may also be potential improvement in the management/treatment of rare cancer patients by centralising them into expert centres, an effect that also needs to be taken into consideration with RWD in this context

RECIST, Response Evaluation Criteria in Solid Tumours; RWD, real-world data; SoC, standard of care.

* Based on the presentations at the workshop by Denis Lacombe (European Organisation for Research and Treatment of Cancer [EORTC], Belgium) and Beate Wieseler (Health Technology Assessment agency, Institute for Quality and Efficiency in Health Care [IQWiG], Germany).

environment, and as long as the first patient is not an adolescent in a first-in-human trial. Finally, the Secured Access to Innovative Medicines for Children with Cancer (SACHA) study is a prospective registry of CU/off-label use of innovative anticancer therapies in children and AYA, initially started in France [22] but now rolled out in Europe, to collect clinical efficacy, safety and PK data, with adequate pharmacovigilance declaration to inform further use and development of these medicines in paediatric and AYA patients aged up to 25 years.

Innovative solutions to improve access to treatments and generate evidence in rare cancers

Real-world evidence (RWE) and prospective registries

RWE based on retrospective data is not generally considered robust as a comparative external control due to multiple confounding effects (Table 2). Historically, retrospective data has been used in submissions to regulators and health technology assessment (HTA) agencies due to a lack of sources of good prospective data, however generating prospective RWD moving forward will facilitate drug approvals and access in rare cancers. In order to address this, the European Organisation for Research and Treatment of Cancer (EORTC) created the large international platform ARCAGEN, an observational study to efficiently gather high-quality prospective data. ARCAGEN recruited ~1,000 patients in 3.5 years from 14 countries via the EORTC SPECTA platform, diagnosed with recurrent/metastatic rare cancer across 10 histologies who provided a tissue/liquid biopsy. EORTC was able to recommend a treatment (either access to a clinical trial or to an existing drug, or an off-label recommendation) for around half of these patients. Therefore, once patient access and regulatory procedures were established, this type of infrastructure could generate volumes of high-quality RWD and access to treatment. Although the outcomes of ARCAGEN were impressive, demonstrating the feasibility of obtaining molecular results with potential new targets for therapy across Europe in a short period of time, there remains the urgent need to move on to interventional trials in rare cancers to generate more robust data systematically.

Building on the success of ARCAGEN, EORTC launches the international infrastructure TRACE (Tracking and Treating Rare Cancers, AYA and Rare Entities in the EU). TRACE combines a prospective registry of focussed groups of rare cancer patients (initially via EORTC SPECTA) including a longitudinal follow-up, while facilitating the rapid conduct of interventional and non-interventional clinical trials, preferably randomised, to allow rapid benchmarking of therapeutic interventions in rare cancers. The cross-talk between registry and clinical research programmes ensures rapid recruitment access through a limited number of highly specialised centres for rare cancer patients and provides access to reliable genomic profiling. Another example of useful evidence generation is SACHA-France, a prospective registry of CU/off-label use in children and AYA, which feeds into the national reimbursement scheme, and could be rolled out across other age groups and other diseases. Such innovative projects bring therapeutic progress to rare cancer patients by embedding a continuum from research to care.

Personalised reimbursement and risk-sharing models

The Drug Rediscovery Protocol (DRUP) framework in the Netherlands is a non-randomised, multidrug, pan-cancer trial platform facilitating off-label treatment access to patients with rare subgroups of cancer whilst collecting data on signals of clinical activity of molecularly matched targeted therapies/immunotherapies [23–26]. As of 2024, more than 2,500 patients were screened in DRUP, with over 1,500 starting treatment, and an overall 16-weeks clinical benefit rate of 33 % [27]. DRUP also aggregates data from other adaptive precision oncology trials to better assess treatment effects. For example, collaboration with the equivalent Australian MoST platform found that CDK4/6 inhibitors have limited clinical activity in tumours with cyclin D-CDK4/6 pathway aberrations [28]. DRUP-like clinical trials (DLCTs) have started/or soon-to-start across 11 countries in Europe under the Precision Cancer Medicine Repurposing System Using Pragmatic Clinical Trials (PRIME-ROSE) consortium (www.prime-rose.eu) [29–31]. Although individual DLCTs are independently governed, PRIME-ROSE facilitates a single entry point for joint negotiations with companies and HTAs, initiatives to improve molecular diagnostics, QoL data gathering from the DLCTs, improving access to off-label medicines, and also explores regulatory pathways for independent research.

Similarly, in Australia, Omico's Precision Oncology Health System Incubator (HSI) model offers a structural solution to extend health outcomes to patients with HUMN. The HSI concept provides expedited access to treatment using pay-for-performance to award industry for drug development costs whilst collecting data to generate value for money estimates. Whilst the safety/efficacy of available therapies has already been established for approval on specific indications, the HSI system collects RWE in off-label indications such as rare cancers to generate health economics data for the HTA process. Preliminary economic modelling has shown that availability at national level of pan-tumour therapies and comprehensive genomic profiling provide outstanding value for money in rare cancers and CUP (David Thomas, Omico, personal communication). Therefore, when dealing with heterogeneous populations for which we have different levels of evidence (e.g. rare cancers), a national framework including reimbursement for access to off-label indications and data gathering should be mainstreamed across Europe and globally.

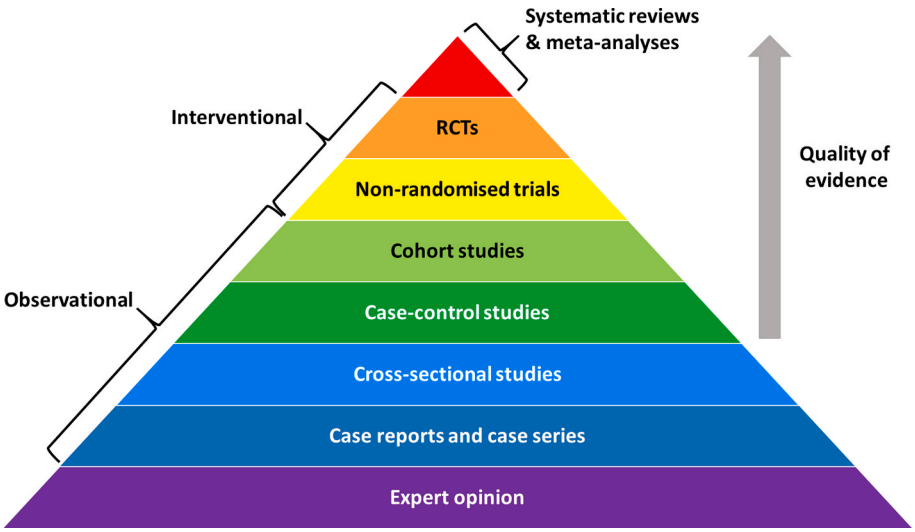

Fig. 1. Evidence-based medicine pyramid: Always aiming for the highest level of evidence. Based on the presentation at the workshop by Denis Lacombe (European Organisation for Research and Treatment of Cancer [EORTC], Belgium). RCTs, randomised controlled trials.

National expert reference centres

Some countries have established nationwide expert centres to optimally manage patients with rare cancers, and others are following suit. For example, sarcoma patients in France have access to NetSARC, an organised network of 26 sarcoma reference centres, including over 35,000 patients with follow-up presented in multidisciplinary team since 2010, under the supervision of the French National Cancer Institute. NetSARC systematically undertakes pathology review of all samples for sarcoma diagnosis, but patients do not need to be treated at a single site. Several studies have consistently shown that managing the nationwide population of sarcoma patients in reference centres is associated with an improved survival [32,33]. The implementation of NetSARC has continued to improve outcomes over the last 15 years for the entire adult sarcoma population (both metastatic and non-metastatic) in France, with a 19 % reduction in the risk of death in the most recently treated cohort (2016–2020) vs older cohorts (2013–2015 and 2010–2012) [34].

Therefore, more national expert networks should be created to optimise the management of rare cancer patients, and where available, centralising patients in reference centres should be prioritised. This coordination to improve access can also be achieved across national boundaries – for example, EURACAN is a consortium of 102 highly specialised European cancer centres, 12 patient advocacy groups and relevant stakeholders that connects patients with rare adult solid tumours to expert healthcare centres across the EU and Ukraine. EURACAN is part of the 24 European Reference Networks funded by the European Commission and dedicated to rare diseases (euracan.eu).

Support from patient organisations

Patients, particularly those affected by rare cancer, and their families want to contribute to clinical research and support access to clinical trials for themselves and others. In a systematic literature review across 33 studies reporting enrolment and recruitment methods, social media advertising resulted in the highest recruitment and enrolment rates in 7 of 20 studies and 9 of 28 studies, respectively [35]. Therefore, awareness campaigns that are targeted and sensitive can maximise clinical trial participation in rare cancers, ideally through patient advocacy groups. Reaching even one or two more patients per region for clinical trial access can contribute significantly to the evidence base in rare cancers.

Patients and patient organisations also have the capacity to support in evidence gathering by collecting and owning data, under the General Data Protection Regulation. Such patient-partnered research approaches may involve patients remotely sharing their clinical information and biospecimens for research (e.g. Angiosarcoma Project [ASCproject]), patient groups establishing biobanks (e.g. Association Française contre les Myopathies [AFM, France], Patient Tumor Bank of Hope, Germany), or even patients being part of governance of a biobank (e.g. Mayo Clinic Biobank, USA) (e.g. [36]. Such a collaborative approach between patient organisations and academics can progress knowledge generation in an under-resourced and slow R&D environment, as well as foster evidenced-based advocacy in rare cancers. Patients can also highlight at EU level the importance of research in rare cancers, emphasising the current inequity in treatment availability for rare cancer patients and the wide survival gap in comparison with common cancers.

Generating robust data, study endpoints and patient-reported outcome measures (PROMs) in rare cancers

HTA perspective for reimbursement

While not all clinical trials can be randomised, we should nonetheless aim for the highest level of evidence for all patients, and address why we are falling short to achieve this for rare cancer patients (Fig. 1). Weak evidence should be avoided if more robust evidence gathering is feasible (i.e. necessity vs choice). For example, when the number of patients included in a single-arm trial is much larger than that in the treatment arm of a respective small randomised controlled trial (RCT), one might wonder why the single-arm trial was not initially designed as an RCT. There is an increasing trend towards single-arm trials and low-quality RWE from observational studies, particularly for HTA submissions in rare cancers. In order to provide high-quality care in a sustainable manner, robust data are required for HTA decision-making which is based on comparative effectiveness and safety (i.e. added clinical benefit) and cost-effectiveness versus standard of care/best available treatment. This highly evidence-based process hinges on a comparison between treatments, making single-arm trials (often submitted with poor-quality external controls from observational studies) highly problematic. Therefore, just because no high-quality evidence is available does not mean that the less reliable methods for evidence generation are valid. From an HTA perspective, the data and study designs must be fit-for-purpose for the research questions at hand.

Panel: Consensus Recommendations & Call to Action on Rare Cancers

1. **Earlier diagnosis is crucial to promote more favourable outcomes as the first step to improve care in patients with rare cancers:**
- Implement dedicated healthcare pathways for faster referrals from primary care into oncology services so that patients with rare cancers present with an earlier stage of disease.
- Implement/reimburse routine molecular diagnostic tools such as comprehensive genomic profiling (CGP) and germline testing to characterise the rare cancer and guide treatment.
- Enable molecular profiling and discussion in molecular tumour boards (MTBs) to increase knowledge and explore therapeutic options in rare cancers.
- Where available, it is beneficial to centralise rare cancer patients into a national expert network of reference centres to provide the best quality of treatment and follow-up, and also rigorously capture outcomes data.
- More national expert networks should be created to optimise the management of patients with rare cancer. National expert networks should mirror the same grouping of rare cancers as the European Reference Networks for rare cancers to facilitate interactions.
- Stronger collaboration and communication between paediatric and medical oncologists to favour adolescents and young adult (AYA) access and enrolment into clinical trials.
2. **Foster innovative strategies embedding a continuum of research to care in rare cancers to streamline treatment access, evidence generation and reimbursement:**
- Encourage recruitment and retention of rare cancer patients into prospective registries to enable intervention trials, facilitate access to clinical trials, and generate robust real-world data (RWD).
- Create national pathways for the access, evaluation and reimbursement of well-established therapies on off-label indications and drug repurposing in rare cancers.
- Use such initiatives to generate not only robust clinical outcomes data, but also health economic data to make convincing arguments to healthcare systems and payers for reimbursement of therapies for rare cancer patients.
- Conduct randomised studies (e.g. randomised adaptive platform trials) in a prospective registry as part of routine clinical practice that enables optimised treatment at market entry, with shorter start-up periods and less cost, i.e. faster access to high-quality evidence-based healthcare.
- Rigorously gather patient-reported outcomes (PROs), notably health-related quality of life (HRQoL) data, as an important aspect in the patient journey for rare cancers by standardising measurements, with mandatory publication of PROs and HRQoL data from trials.
- Continue to strive for high-quality data in rare cancers, despite small patient numbers in trials, in order to optimise regulatory submissions for new indications.
- Through advocating the adaptation of the legislation and updating the compassionate use (CU) guideline to allow for collection of RWD, create a clear and harmonised framework on how to use RWD in global CU programmes so that RWD generated outside of clinical trials are collected consistently to generate evidence.
3. **Streamline and harmonise regulatory procedures to speed up access to treatments in rare cancers across the EU:**
- Create a harmonised framework for CU in Europe including consistent terminology (only one term for CU) across Europe, and increase awareness of CU availability through a Europe-wide database (such as FDA's clinicaltrials.gov) in order to foster clarity and simplify the CU process for industry to deliver early access to rare cancer patients in Europe.
- Preserve the European regulatory orphan drug ecosystem so that any revision of the EU Pharmaceutical Legislation does not undermine the incentives of industry to develop orphan drugs to treat rare cancers.
- Abolish the'18-year dogma' – Foster regulatory flexibility at the national, pharmaceutical and clinical level as much as possible and as is clinically appropriate to ensure AYA inclusion in a relevant trial and increase the numbers of joint adolescent-adult early phase trials.

Greater collaboration amongst all stakeholders to remove the roadblocks for the development of new treatments for rare cancers in Europe:

- Collaboration locally, nationally and internationally to aggregate patient numbers, generate more robust data and share knowledge.
- Collaboration in international settings with cooperative groups and experts in clinical research methodology to enable practice-changing research.
- Collaboration with patient expert groups to be involved in clinical trial design, recruitment, and retention. Patient groups are also essential for the dissemination of the results, and patient representatives may be co-authors on publications.
- Collaboration between the relevant academic/industry groups to increase AYA tumour biology knowledge, share data produced in molecular profiling programmes, and increase molecularly-driven trials allowing the full age spectrum.
- Collaboration between regulatory, health technology assessment bodies, payers and industry on shared responsibility for consistency in high-quality evidence generation, trial methodology and cross-border access.
- Collaboration between governments, charities and funders to foster investments into rare cancer research and development by creating more grant opportunities for academics and to incentivise industry in Europe.

The debate over RCT, overall response rate (ORR) and acceptable uncertainty

Conducting RCTs in smaller populations is challenging and sometimes unfeasible, leading to the question of whether treatment availability in rare cancer must always be based on RCT data, particularly if the signal of activity is evident from Phase 2 (e.g. [37]. Similarly, although ORR is not considered to be a clinical benefit measure by regulators, in situations of HUMN (i.e. rapidly progressive disease, no other treatments), a treatment causing significant tumour shrinkage may still be considered useful by patients and oncologists. An EMA survey of global regulators and haematologists found that favourable ORR data from a single-arm trial complemented by high-quality RWD showing a survival difference of 3 months was almost as convincing as an RCT showing just ~1.5 months' improvement for granting a conditional marketing authorisation (Francesco Pignatti, personal communication). Therefore, different approaches to evidence generation may overcome the challenges associated with drug development in small populations, including high-quality external controls based on RWD.

Preconceptions about what is considered acceptable vs unacceptable

uncertainty in clinical oncology may not necessarily apply to rare cancers [38]. For example, in large pivotal studies for common cancers (e.g. melanoma), 30 % ORR with a new treatment is considered acceptable at the population level, leading to its approval even though the majority of patients will in fact not respond. Similarly, a large pivotal RCT in lung cancer may show improved survival with a drug leading to its approval, despite the inclusion of various histologies – yet if the same trial design yielded the same results across various rare cancers sharing a common biomarker, regulators would demand further data by histotype. This raises the question of why we accept uncertainty in one situation but not in the other, if in each case the gap between survival curves for control and experimental arms shows a similar significant benefit with the new treatment. There appears to be a lack of acceptance from regulators, and as a result also industry, about tolerating known uncertainties such as histotypes in frequent cancer but not in rare cancer. A major challenge in the field of rare cancers is the application of 'classical methodology' in a different paradigm to that of common cancers. Finally, as a community, it is important to consider patient preferences and risk attitudes in situations of HUMN.

PROMs

The patients' perspective is also crucial for evidence generation, including on how a new treatment will affect day-to-day life, particularly in rare cancers in which we must extract as much evidence as possible from every patient available. Health-related quality of life (HRQoL) is one of the best-known patient-reported outcomes and is often used as an endpoint of clinical studies. Yet, remarkably, there is very little information on the HRQoL of patients with rare cancers in general, despite the shattering impact of receiving a rare cancer diagnosis on patients' physical and emotional functioning [3,39,40]. In addition to an often delayed and complex diagnostic pathway, patients with rare cancers also face specific challenges during the therapeutic trajectory (e.g. access to expert care and drugs). Currently, the EORTC Quality of Life group runs a project to establish the optimal strategy to measure relevant aspects of HRQoL of patients with a rare cancer participating in a clinical study [41].

Conclusions

Patients with rare cancers, including AYA, have long been neglected in terms of access to treatment – whether it be slow referral to an oncologist leading to late-stage presentation, the lack of R&D funding, missed opportunities for evidence gathering, or overly complex EU regulatory pathways. There is an urgent call for collective effort across all stakeholder groups for new EU-specific solutions to raise the standard of care for this patient group that has long been left behind. In order to drastically change the current paradigm for the management of rare cancer patients, new partnership solutions between public and private sectors must be explored to incentivise funding initiatives while placing rare cancer patients at the centre of discussions. Notably, we need greater public investments in common non-competitive dedicated infrastructure, such as integrated observational or interventional platforms informing on disease natural history and raising hypotheses to sustain clinical research questions. Finally, more than ever, access to biomarker testing is a critical first step in the patient journey to expedite their access to precision oncology treatments.

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