Virchows Archiv (2025) 486:207–214
https://doi.org/10.1007/s00428-024-04005-1

REVIEW

The role of the pathologist in the design and conducting of biomarker-driven clinical trials in cancer: position paper of the European Society of Pathology

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Received: 25 October 2024 / Revised: 2 December 2024 / Accepted: 4 December 2024 / Published online: 17 December 2024
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Abstract

Clinical trials in oncology are important tools to identify and establish new effective drugs for cancer treatment. Since the development of the concept of precision oncology, a huge number of multi-centric biomarker-driven clinical trials have been performed and promoted by either academic institutions or pharmaceutical companies. In this scenario, the role of pathologists is essential in multiple aspects, with new challenges that should be addressed. In this position paper of the European Society of Pathology, the role of pathologists as contributors to the design of the clinical trial, as local collaborators, or as members of central review laboratories is discussed. Moreover, the paper emphasizes the important role of pathologists in guiding methods and criteria of tissue biomarker testing in the biomarker-driven clinical trials. The paper also addresses issues regarding quality control, training, and the possible role of digital pathology.

Keywords Pathology · Clinical trials · Predictive biomarkers · Quality control · Window of opportunity trials

Introduction

New cancer cases rose by 2.3% in 2022 compared to 2020, to reach 2.74 million in 2022 in Europe. Similarly, cancer deaths went up by 2.4% compared to 2020, according to the European Commission's estimates [1]. The European Union Clinical Trials Register currently displays 43.992 clinical trials with an EudraCT protocol, of which 10.564 are conducted with cancer patients [2].

Clinical trials are important tools for implementing drugs in the clinical management of patients. They serve as the bridge between promising pre-clinical discoveries and their safe and effective implementation in patient care. A clinical trial in oncology is a research study investigating the safety and effectiveness of an intervention to potentially improve outcome for patients with cancer [3–5].

Clinical trials rely on multidisciplinary teams. Pathologists have always played an important role in clinical trials [6], by providing pathologic diagnosis and staging, as well as results of various ancillary tests of various tissue biomarkers providing prognostic and predictive information.

Clinical trials use drugs that have been identified and previously investigated in in vitro or more recently in in silico models [7] using cell biology approaches and subsequently confirmed their efficacy in animal models in the settings of *pre-clinical research* studies.

Clinical trials test new treatment approaches and follow a process from phase 1 to phase 4.

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Phase 1 clinical trials focus mainly on evaluating the safety and tolerability of a new drug or treatment in a small group of healthy volunteers or patients with cancer. Dose escalation is usually carried out until intolerable clinical toxicities ensue, defining the maximal tolerated dose and establishing the optimal dose for phase 3 studies.
Phase 2 clinical trials focus on effectiveness and side effects in an extended cohort of predefined patients. These trials aim to determine whether the treatment has expected anti-tumor activity and to further evaluate its safety.
Phase 3 clinical trials compare the safety and effectiveness of the new treatment against the current standard of care approaches. If the new treatment proves superior or offers significant advantages, it may then be considered for regulatory approval.
Phase 4 studies, after the drug is approved and made available to patients, where the long-term effects of the treatment are monitored, under real-world clinical testing and treatment.

With the emphasis on a personalized medicine approach in oncology, the original concept "one size fits all" of treatment is now more and more replaced by a tailored therapy for each patient based on specific features of both the patient and the tumor. To better stratify malignant tumors, the original approach using histological typing, microscopic grading, and TNM staging has been complemented with testing of various molecular biomarkers more precisely characterizing the individual tumor and providing the information about its signaling pathways, which can be used for targeted treatment. The number of biomarkers in clinical practice has been growing, and around 55% of all oncology clinical trials in 2018 involved the use of biomarkers, as compared with 15% in 2000 [8]. Testing of biomarkers in clinical trials is driven by the mechanisms targeted by precision therapies and immunotherapy and serves mainly for the selection of the best candidates for the tested treatment.

As some genomic alterations (mutations or gene fusions) may show very low incidence in certain cancer types (e.g., NTRK fusions are identified in 0.2% of all non-small cell lung cancer cases) [9], it would be very challenging or even impossible to collect statistically significant results if the traditional design of clinical trials would be used. Therefore, for biomarker-driven clinical trials, two additional formats have been introduced:

A *basket trial* enrolls patients with different types of cancer who share a common biomarker (specific mutation, gene fusion, protein expression, etc.), rather than focusing on a single tumor type. This approach allows for the evaluation of a targeted therapy across multiple cancer types, namely in the case of rare targets, where conducting a trial with classical design would be very challenging or even impossible, thus potentially accelerating drug development and identifying new indications for existing therapies.

An *umbrella trial* enrolls patients with a single type of cancer but with different therapeutically relevant genomic alterations (mutations, fusions) or biomarker profiles. Multiple targeted therapies are evaluated simultaneously within the trial, allowing for the identification of the most effective treatment for specific patient subgroups.

Beyond basket and umbrella trials, other innovative formats are being explored to optimize the evaluation of targeted therapies and enhance personalized treatment strategies. These include adaptive trials, which allow for modifications of the trial design based on interim data analysis; platform trials, which utilize a master protocol to evaluate multiple treatments simultaneously; and N-of-1 trials, which focus on individual patients to assess personalized therapies [10–12]. These diverse trial designs reflect the growing emphasis on precision oncology and the increasing complexity of biomarker-driven research, offering the potential to accelerate drug development, identify new therapeutic targets, and ultimately deliver more personalized and effective cancer treatments.

Novel molecularly based anticancer treatments are often investigated in end-stage patients first. This approach is based on the ethical principle "*Primum non nocere*"—"Above all, do no harm"—and in this context, innovative treatment under investigation is given to patients with no other approved or guideline-based therapeutic options. However, as cancer in the final stage may significantly differ from the earlier stages, this approach may not provide the most relevant data. Therefore, another concept called *window of opportunity clinical trials* has been introduced, where patients receive the drug between the cancer initial diagnosis and primary surgery [13]. Comparative analysis of the tumor features (morphology and molecular features) in initial tumor biopsy and resection specimen (presumably resulting from effects of the investigational treatment) provides biological evidence for the possible effect of the drug in a specific group of patients. For the evaluation of such a trial, the comprehensive pathologic evaluation of the tissue in biopsies and resection specimens is essential.

Clinical trials are often conducted with specific patient populations, in specialized academic environments that may more or less differ from routine clinical practice, and the number of patients included in the trial is always limited. Moreover, the trial inclusion criteria are specifically designed to create a highly selected trial population to show the superiority of the drug, which might not reflect the average patient population, leading to inferior real-world performance (or also higher survival rates of the control population than average). Thus, the later use of *real-world data* is crucial to understand the utilization

patterns and outcomes of new treatments in clinical practice [14–16].

Pathologists are also involved in observational studies, cross-sectional studies, and cohort studies, but their role in these clinical studies is beyond the goal of this position paper.

Statement 1: Pathologists' expertise is crucial to interpret the results of the different types of clinical trials exploring the effects of new drugs in patients with cancer, from pre-clinical research studies through different types of traditional and biomarker-driven clinical trials to real-world analysis.

Role of the pathologist in pre-clinical studies

Pre-clinical studies test drugs that might have an impact on the tumor in a number of situations. Most of the experiments are performed in cell cultures by monitoring the effects of the drug on cell viability, apoptosis, proliferation, wound healing, and other parameters, in tumor cells. 3-D cultures and patient-derived tumor organoids represent interesting tools. But frequently pre-clinical studies involve animal models, either genetically modified animals [17, 18], cell-line derived xenografts [19], and/or patient-derived xenografts in nude mice [20, 21]. The effect of the drug is assessed by the pathologic features of tumor tissue, and changes in biomarker expression, after treatment. In the case of genetically modified animals, pathologic evaluation requires veterinary pathology expertise, with previous training on the normal structure and variability of the animal tissue. In the case of patient-derived xenograft models, pathologic analysis should take the specific features of the animal tumor microenvironment into account, which in principle differs from its human counterpart.

Statement 2: In pre-clinical studies with animal models, pathologic expertise in the interpretation of the tumor tissues after the administration of the drugs provides an essential insight in the precise effect of the treatment. This may represent an opportunity for academic pathology to establish/provide structured and quality-assured patho-histological analysis of research animal histology for clinical trials and beyond.

The role of the pathologist in conducting clinical trials

In recent decades, pathologists have become important players in the conduct of clinical trials, particularly in biomarker-driven clinical trials.

The involvement of the pathologist is very important in different phases, depending on the specifics of the clinical trial [6]:

Trial planning and protocol development, by defining diagnostic criteria, adequate staging criteria, and criteria for target detection (biomarkers to be tested, establishment and validation of tissue-based diagnostic assay, tissue-relevant information) to be provided to trial participants.
Stratification (trial-related tumor diagnostics) and identification of eligible patients: by performing tumor typing, pathological staging and grading, and analysis of trial-relevant biomarkers. These analyses may be performed decentralized (using local pathology facilities, methods, and technology platforms) or centralized or in a combination of both (e.g., used for stratification, selection of the best method used for testing, and definition of criteria for evaluation of biomarker results).

The pathologists may/should have additional essential roles, such as (1) being part of advisory boards supporting the planning conduct and evaluation of clinical trials, (2) in performing/advising tissue-based trial-accompanying research, and (3) in biobanking of tissue samples acquired in the context of clinical trials.

In general, the pathologist may have three different roles in clinical trials:

- As a member of the team in planning and/or advising of the trial
- As a local collaborating pathologist, providing pathologic data and tissue samples
- As a central/reference pathologist in central review or providing central tissue-based analyses

The most frequent role of the pathologists in a clinical trial is as a *local collaborating pathologist*, providing accurate trial-related diagnostics and trial-related tissue information of the patients that may be recruited in the clinical trial, but also frequently, by taking care and providing tumor tissue samples to be sent to a reference laboratory, for diagnostic confirmation, as well as performing additional exploratory immunohistochemical and molecular tests of biomarkers used for inclusion/exclusion in the trial or for the randomization purposes.

Clinical trial diagnostics represent a growing and rewarding translational research field in pathology, and some pathology departments have their own diagnostic trial units that take care of the different trial-related processes, depending on their professional trial involvement: (1) scientific review of the protocols prior to institutional review board (IRB) submission; (2) control of ethical requirements,

including confirmation of signed informed consents; (3) budget development; (4) feasibility assessments; (5) sample procurement, processing, and storage; (6) sample shipment fulfilling the standards of Good Laboratory Practice; (7) inventory maintenance of study kits; (8) pathologic data record; (9) protocol amendment review.

There are important points of improvement for the role of the pathologist as a local collaborator in clinical trials:

- *Recognition of local pathologists' work*, since their contribution is usually not appropriately recognized in the contract between the trial organizer/sponsor and the corresponding hospital. There is infrequent recognition in manuscripts arising from the clinical trial. Ideally, the list of local collaborating pathologists should at least appear in the supplementary material of the final manuscript.
- *Scientific feedback*. The local pathologists do not usually receive feedback of their contribution to the clinical trial, for example regarding the reproducibility of the pathologic and biomarker testing results with the central reference laboratory. It is important to point out that trial-related diagnostics do not suffice regular diagnostic needs and that diagnostic responsibility lies and remains with the local pathologist. Moreover, many clinical trials do not have strategies to address differences between regular diagnostics and trial-related analyses.
- *Financial compensation*. Pathologists' workload is usually calculated by the type, complexity, and number of pathologic specimens received in a pathology department, in a specific health center, without considering the extra work generated by an increasing number of clinical trials. The work of the pathologist, specifically in the clinical trial, as well as the work in managing the specimens, back and forth, should be taken into account when signing the contract between the trial organizer/sponsor and the hospital. The department of pathology should have an important role in quantifying data (man-hours, extra material cost) for the economic part of the trial contract. Overhead costs should also be adequately considered,
- *Tissue contribution*. Tumor tissue is predominantly kept as formalin-fixed, paraffin-embedded (FFPE) tissue blocks. Since the appropriate follow-up clinical management of the patient might require future additional tests, it is important to ensure that in case routine tissue material is taken, a sufficient representative amount of tumor tissue is kept in the archives of pathology departments, once the tumor tissue has been sent to the central testing in a reference laboratory. This can be achieved in different ways: (1) by providing tissue sections, rather than paraffin blocks; (2) by dividing paraffin blocks; (3) by ensuring that there are other informative paraffin blocks; (4) by making sure that paraffin blocks are returned from the central reference laboratory, once the clinical trial is finished.

In addition, the pathology clinical trial units are sometimes also asked to recruit materials other than FFPE material such as blood for liquid biopsy analysis or frozen tumor tissue for a number of processes such as generation of patient-derived organoids, isolation of immune cell components, or other procedures. This represents an additional burden for the department of pathology with many limiting aspects, which are out of the scope of this paper.

Statement 3: It is important to recognize the role of the local collaborator pathologist in clinical trials, by ensuring scientific recognition, results, and feedback and by considering the economic consequences and the responsibility of keeping appropriate informative tumor tissue in the local center for possible future biomarker testing for further clinical management. Participation in clinical trials should represent a relevant, rewarding, and growing translational research field for pathology institutes and a core expertise of pathology.

Pathologists are also involved in *central reference laboratories*. They may be linked to academic centers, closely related to the group of clinicians involved in the design or lead of the clinical trials, with proven experience in the tumor type or biomarker analysis that are subject of the clinical trial. Quite frequently, however, these central reference laboratories may be represented by private laboratories with demonstrated experience in handling tissue samples from clinical trials and contractual relation with the pharmaceutical company sponsoring the clinical trial. In both cases, the central laboratory provides validation of the pathologic and biomarker testing results of the local pathology collaborators or central testing. There are some important aspects to be considered:

- The central reference laboratory (either academic or private) should be clearly mentioned in the manuscript providing the results of the clinical trial, for reasons of transparency.
- The central reference laboratory should demonstrate not only high-level experience in handling tissue specimens in clinical trials but also specific knowledge (publication record) in the pathology of the tumor type or the biomarker analysis of the study. If this tumor-specific knowledge is lacking, it is recommended to involve respective internationally recognized expert pathologists into the clinical trial.
- The reference center should provide scientific feedback and return the unused tumor tissues to the local collaborator pathologist.

Statement 4: It is important to adequately address the role of the central reference pathology laboratory in clinical trials, by providing appropriate information in the manuscript with the results of the clinical trial. It is important for a central reference pathology to guarantee experience in handling tumor tissue in clinical trials, but also ensure specific knowledge in tumor pathology and/or biomarkers that are the subject of study. The central reference pathology laboratory should provide results and feedback to the local collaborator pathologists and take care of returning unused remaining tumor tissue to the local center for possible future clinical management.

Role of pathologists in the design of biomarker-driven clinical trials

The design of oncologic clinical trials is a complex process that involves the promoter/sponsor (academic or pharmaceutical company) as well as oncologists and a number of other specialists involved in methodology. Historically, pathologists have not been part of the team involved in the design of clinical trials.

The pathologist may also play a critical role in conducting exploratory research either independently or in collaboration with sponsors to identify biomarkers, as obtained results may be important for the design of new clinical trials.

Pathologists with expertise in the tumor type subjected to the clinical trial may help in defining inclusion criteria. Occasionally, clinical trials may still include patients solely based on the anatomic location of the tumor and ignoring the tumor biology (such as a study recruiting all patients with non-small cell lung cancer, patients with all types of breast cancer, kidney cancer, etc.). Pathologists are aware of the fact that tumors from the same organ may have different biological features depending on the microscopic appearance (histologic subtypes) or molecular features. The inclusion of diverse or unusual tumor subtypes in these clinical trials may contribute to inconclusive data. The pathologists' expertise may help to reflect current knowledge of tumor biology and thus optimize inclusion criteria for obtaining more reliable results.

Intra-tumor heterogeneity is an important feature that is usually not taken into account when defining inclusion criteria in a clinical trial. Pathologists experience it in their daily diagnostic practice and reporting. Not exceptionally, tumors are composed of a combination of two or more tumor components, each of them having different biological features. Such intra-tumor heterogeneity may be the consequence of tumor evolution and progression and may be detected in different areas of the primary tumor, or when comparing the primary tumor with its metastases. This intra-tumor heterogeneity might also be detected at the biomarker level, for example for HER-2 or PD-L1 expression or for mismatch repair gene status, when tumors may contain tumor subpopulations with different patterns of alteration of these pathways. From the pathologist's viewpoint, it is obvious that these tumors may respond to a drug, in a way that depends on the different proportions of each component. The inclusion of a pathologist in the trial design team may help in establishing criteria on how to handle these cases.

The definition of the best predictive tissue biomarker as well as the method(s) selected for its testing is of utmost importance for the optimal design of the clinical trial. It is very important to keep in mind that a good predictive tissue biomarker should be analyzed by a technically feasible test (under real-world diagnostic constellation), and results and scoring should be reproducible. The opinion of an expert pathologist may avoid inappropriate decisions that put the feasibility and reproducibility of the predictive biomarker testing at risk. The search of the best predictive test should be done by considering all possible biomarkers and techniques by following scientific means and criteria.

It is important to take into account that there are commercial agreements between pharmaceutical and biotechnological companies, and also regulatory requirements, that may have an impact in the initial decision of selecting the diagnostic assay to be applied in a clinical trial. Even in this scenario, the expertise of an experienced diagnostic pathologist may minimize the risk that biomarker testing may be technically unfeasible in the future, when (after the success of the trial) the new treatment is implemented into routine clinical practice. The pathologist may also have an advisory role about regulatory requirements.

Although this is an evolving issue, some scientific associations, such as GCIG (Gynecological Cancer International Group), have already emphasized the important role of pathologists in the design of biomarker-driven clinical trials [22].

Statement 5: It is recommended that pathologists are part of the team involved in the design of clinical trials in cancer, particularly in biomarker-driven clinical trials. Pathologists with proven expertise in the tumor type subjected to the study may support in defining inclusion criteria (avoiding inappropriate inclusion of tumors of different biological features) and specific criteria for tissue handling and, more importantly, help in defining the best predictive tissue biomarker assay and scoring.

Quality control

Any laboratory method, including those used for biomarker testing, is subjected to variability in technical performance and interpretation. For that reason, it is important to ensure that local collaborating pathologists and central reference

laboratories fulfill the standards of Good Laboratory Practice and quality control in both technical performance and scoring [23, 24]. Generally speaking, the participation of local laboratories and central reference laboratories in external quality assurance schemes should be required, at least for well-established biomarkers. Accreditation by ISO 15189 standard or similar is recommended for the central reference laboratories and advisable for participating local laboratories.

Statement 6: Quality assurance in pathology clinical trial performance, as well as regulatory compliance, is important. It is necessary to ensure reproducible tissue handling, biomarker analysis, and reporting of tissue-based pathology parameters in the pathology departments participating in the clinical trial.

Training pathologists

Pathologists are vital to the success of tissue-based clinical trials. It is important to ensure that the pathology personnel involved in clinical trials undergo specific training relevant to their role [25]. Optimally, training for specific procedures required in clinical trials should be provided to all pathologists and pathology technicians, since every practicing pathologist, pathology trainee, and pathology technician eventually may be involved in providing services and data to clinical trials.

Statement 7: Pathologists and pathology technicians involved in clinical trials should have training in the main concepts related to clinical trials.

Digital pathology

The incorporation of digital pathology (DP) tools into pathology will have an important impact on improving the development and design of biomarker-driven clinical trials [26]. Digital transformation of pathology departments not only represents the acquisition of scanners, computers, and screens but also has an impact on improving the pre-analytical management of tissues and full traceability of the specimens. Although this is an evolving area, one of the main limitations of the incorporation of digital transformation in the pathologic assessment of samples in clinical trials is the limited access to DP equipment in pathology departments in Europe. This limitation has to be addressed.

One of the most relevant advantages of the digital transformation of pathology departments is the possibility of sharing whole slide images (digital slides) between centers, in the so-called telepathology. This is a key component of central reviewing strategies.

Another advantage of DP is the fact that digital slides can be further analyzed by different types of software focused on quantitative or qualitative measurement of various features. There are a number of image analysis algorithms to assist standardization of biomarker reporting by pathologists. The vast majority of these algorithms are still undergoing validation and thus are not ready for routine use; however, some of them are already FDA- and CE IVD-cleared and can be utilized in clinical practice.

Additional aspects to be considered are (1) regulatory considerations, clear regulatory guidelines are needed to ensure the safe and effective implementation of digital pathology in clinical trials and routine clinical practice; (2) data management and security: robust data management systems and security protocols are essential to protect patient privacy and ensure data integrity; (3) quality assurance: DP aspects of clinical trial management have to be included into the existing quality assurance measures (see above).

Image analysis algorithms may play a significant role in documentation and assessing pathologic parameters (tumor cell content, immune cell components, and others) that are subjected to high inter-observer variability.

Statement 8: Digital pathology tools are helpful in clinical trials, especially in central reviewing, documentation, and training. Image analysis, particularly for biomarker quantification, may have a role, whenever proper validations have been performed. The use of such algorithms in the clinical trial and their impact on the implementation of biomarker tests into routine practice has to be considered.

Role of pathologists in the interpretation of real-world data

The term real-world evidence [14–16] refers to information on health care that is obtained from different sources (patient registries, electronic health records, claims and billing data, product registries), which complements the knowledge derived from traditional clinical trials. Real-world data have high external validity due to the inclusion of a large number of patients in routine care, allow for long-term follow-up of patients, and also provide information on how factors such as clinical setting and provider and health-system characteristics influence treatment use, effects, and outcomes.

Incorporating pathologists in the team interpreting the results is essential for qualified, reliable, and unbiased interpretation of the real-world pathologic data and their comparison with the pathologic data from the trial. This may also include (1) real-world implementation and quality of biomarker testing as a key factor for drug success, (2) eliminating trial biases, and (3) including collection of pathology data in clinical/cancer registries.

Statement 9: Real-world data are important to confirm the results obtained in randomized clinical trials. Incorporation of pathologists in the team interpreting real-world evidence is essential for the correct analysis of the data.

Conclusion

The evolving landscape of cancer research, with its increasing emphasis on precision medicine and biomarker-driven clinical trials, has placed the role of the pathologist into the spotlight. The pathologist's expertise is no longer confined to the diagnosis but extends to every stage of the clinical trial process, from design and patient selection to data interpretation, post hoc analysis, and trial monitoring. As the field moves towards increasingly personalized cancer therapies, the demand for pathologists in clinical trials will increase even further. The pathologist's ability to integrate molecular findings in the appropriate clinico-pathologic context and to close the gap between complex molecular data and clinically actionable insights is essential for trial success and optimizing patient care.

Author contribution Xavier Matias-Guiu wrote the initial draft. All authors edited it.

Declarations

Ethics approval Not required.

Conflict of interest The authors declare no competing interests.

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