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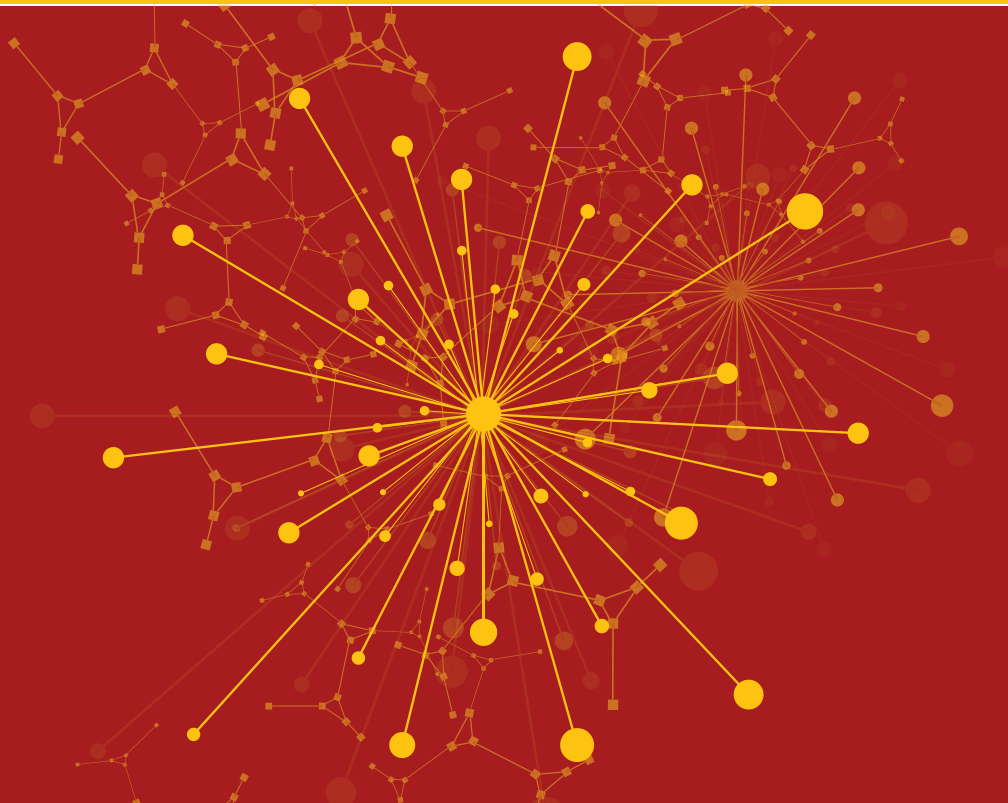
Medical Education

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FUNDAMENTALS OF DESIGNING CLINICAL TRIALS

Part 2: Contemporary designs of phase I and II trials in oncology including endpoint selection and quality of life as an endpoint

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Preface

Dear Colleagues

Due to the innovations in the field of oncological treatment that have profoundly changed our perception of modern cancer therapy, the design of clinical trials had to be modified appropriately with the purpose of allowing for the assessment of the distinct effects of new drugs. This means that long-standing paradigms had to be abandoned, and new principles took their place. In light of continuing research, which happens at breathtaking speed, this process is still ongoing.

As the size and complexity of phase I trials have been increasing over time, investigators are facing considerable challenges these days. On the other hand, the investigational process can be shortened significantly if patient selection and assessment of treatment efficacy are conducted from the very beginning. Phase II studies used to provide initial assessment of efficacy, but adaptive trial designs in the setting of targeted therapy often lead to amalgamation of phases I and II.

Endpoints play a major role in the design of clinical studies and should therefore be selected carefully. The use of quality-of-life assessments adds valuable information to the data delineating the strengths and weaknesses of a certain treatment.

Given the recent developments, the articles presented in this paper are aimed at updating the reader on aspects of the contemporary designs of phase I and II trials, with an emphasis on endpoint selection and the use of quality of life as a trial outcome. We hope to provide useful information that might contribute to supporting scientific efforts on our way towards finding a cure for cancer.

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Phase I trials

Drug development trials are traditionally divided into 3 phases serving different purposes (**Table 1**). Phase I assessments, which represent the first-in-human evaluation of any new compound, focus on determination of the optimal dosing for further testing. Primary endpoints therefore typically include dose-limiting toxicities (DLT), the maximum tolerated dose (MTD), and the recommended phase II dose. Secondary endpoints comprise pharmacokinetics (PK), pharmacodynamics (PD), and preliminary anti-tumor activity. Patients, rather than healthy volunteers, with refractory cancer of any type are eligible.

Phase I trials consist of the dose escalation portion and the cohort expansion portion. The dose escalation part is dedicated to assessment of PK, safety and MTD. This segment usually encompasses only very few patients for each of several dose levels. In the expansion phase, a greater number of patients is recruited into one or two selected dose levels with the purpose of decreasing confidence intervals. Adverse events (AEs) of cytotoxic chemotherapy usually become evident within the very first treatment cycles.

Changes brought about by the introduction of targeted treatments

The principles of designing oncology phase I trials have changed in the context of targeted therapies, which nowadays constitute the bulk of investigational drugs. Targeted agents need to be administered for longer periods, often without the frame of defined cycles. Also, toxicity follows a different pattern. According to a review of 36 phase I trials conducted with targeted therapies, the majority of severe AEs only becomes apparent after cycle 1, and 50 % of patients experience their worst-grade toxicity after completion of the customary DLT assessment period [1]. Moreover, targeted therapies usually show no dose-response-relationship in the phase I setting, which renders determination of the ideal dose difficult.

All things considered, MTD and DLT might be concepts of the past that no longer apply to modern drug development, and their definitions need to be reconsidered. Another aspect is the choice of PD markers in the targeted era, as the optimum target inhibition, and thus the optimum sample size, is usually unknown. Mostly, tumor tissue is used to determine PD markers.

A major difference between phase I studies for cytotoxic drugs and those for targeted compounds relates to the amount of early efficacy data. With chemotherapy, the focus used to be on safety rather than on anti-tumor activity, and as several types of tumors were treated, conclusions about certain types of tumor that responded particularly well were difficult. Many targeted agents that have been tested over the last 10 to 15 years, however, showed response rates of more than 50 % in the phase I setting. This development has become possible due to the improved understanding of tumor biology. At present, many oncology phase I studies are no longer involving patients with any cancer type, but instead those who appear most suitable for the new drug.

Advantages of multiple expansion cohorts

All of these changes have led to considerable increases in the size of cohorts involved in phase I trials, the number of expansion cohorts, and the objectives of the studies (**Table 2**). A typical example is immunotherapy trials that tend to comprise 6–8 or even more expansion

TABLE 1 Characteristics of traditional phase I, II and III drug development trials			
	Phase I	**Phase II**	**Phase III**
Purpose	Identification of MTD	Definition of activity	Comparison with standard of care
Emphasis	Safety	Activity	Efficacy
Endpoint	Toxicity (DLT)	Response (ORR)	Survival (PFS, OS)
Patients (n)	20–60	20–200	200–2,000
Registration value	Null	Limited	Major

MTD, maximum tolerated dose. DLT, dose-limiting toxicities. ORR, objective response rate. PFS, progression-free survival. OS, overall survival.

TABLE 2 Increases in size and complexity of phase I studies over time		
1990–2005: 30–40 patients, e.g. chemotherapy	**2005–2010: 50–100 patients, e.g. targeted therapy**	**2010–present: 200–400 or more patients, e.g. immunotherapy**
Dose-escalation (usually one schedule)	Dose-escalation (potentially with alternative schedules)	Dose-escalation often starting at minimum anticipated biological effect level (MABEL) dose
Single expansion cohort (n = 10–18) for safety/PK	3–4 small expansion cohorts (n = 10–18) for (1) safety/ PK, (2) biopsies for PD, and (3) antitumor activity in 1–2 biomarker-selected patient groups	6–8 (or more) large expansion cohorts (n = 20–40+) for (1) safety/ PK, (2) biopsies for PD, and (3) antitumor activity across multiple tumor types

TABLE 3

Challenges resulting from the inclusion of multiple expansion cohorts in phase I trials

Planning	Implementation	Execution
Requirement of significant upfront planning and resources by study sponsor, including drug supply and assays for predictive biomarkers	Phase I units are required which coordinate well with disease-area clinics	Size and complexity of multiple cohorts enrolling simultaneously place a strain on sites and contract research organizations
Evolving of clinical data often results in multiple amendments	Global studies often have different country-specific requirements	Requirement of a robust safety monitoring plan and enhanced communication with sites
Systems (Interactive Response Technology, electronic data capture systems etc.) need to be designed with flexibility in mind	Increased questions from health authorities and institutional review boards who might only partially approve a study with a view to pending additional data	

cohorts, which enables the testing of different doses and schedules in different tumor types. According to an analysis by Mullard et al., recent industry-sponsored phase I trials on immunotherapies included as many as 1,000 to 2,000 patients, thus drawing level with the traditional size of cardiovascular studies [2].

The inclusion of multiple expansion cohorts in phase I trials allows for simultaneous assessment of drug activity and evaluation of predictive biomarkers across various tumor types as well as further cohort expansion when promising efficacy signals occur. Also, multiple expansion cohorts lead to rapid enlargement of safety databases and speed up the drug development process for clearly efficacious drugs, which thus can benefit patients early on.

Challenges due to multiple expansion cohorts

On the other hand, there is a number of unique complexities and challenges with respect to planning, implementation and execution (**Table 3**). Protocols must be amended due to emerging data, sometimes repeatedly. An example of this is the KEYNOTE-001 trial [3] evaluating pembrolizumab in melanoma that underwent eight amendments, in the course of which the total sample size rose from 32 to 1.067 patients. Amendments often need to be implemented at different sites across the world, as these huge phase I trials are frequently conducted globally. In contrast, classical phase I studies used to be restricted to one site.

Concerns have been uttered that the changes in design and objectives will hamper the quality of safety data obtained in phase I. In their article on seamless oncology-drug development published in the New England Journal of Medicine in 2016, Powell et al. posed a range of questions regarding the design of large first-in-human cancer trials (**Table 4**) [4]. ■

TABLE 4

Questions regarding the design of large first-in-human cancer trials

Is there a compelling rationale for including multiple expansion cohorts?
Is the sample-size range consistent with the stated objectives and endpoints?
Is there an appropriate statistical analysis plan for all stated endpoints?
Are the eligibility criteria appropriately tailored to the expansion cohorts?
Is there a defined end to the trial, in terms of both efficacy and futility?
Is there a system in place to communicate with all investigators in a timely fashion?
Does the informed consent reflect the current knowledge of safety and efficacy of the investigational drug and other agents in the same class?
If the trial may be used for regulatory approval, is there an independent oversight committee?
If the trial may be used for regulatory approval, has there been communication with regulatory agencies?

Take home message

Traditionally, oncology phase I trials used to focus on safety and the determination of the optimum phase II dose. In the era of targeted agents, the dose expansion part has changed, as improved understanding of the tumor biology allows for accurate patient selection from the very beginning. Anti-tumor activity as assessed in the phase I setting is no longer preliminary, and the sizes of cohorts have increased monumentally. This allows for shortening of the investigational process, but at the same time, it increases the complexity of planning and implementation.

Gilberto Schwartsmann

Phase II trials

Phase II studies provide initial assessment of efficacy in a more homogeneous patient population. Screening out of ineffective drugs is an objective here, as is the identification of promising new agents for future evaluation. The activity of a compound is assessed in a given tumor type, which allows for selection of tumor types for further study. Also, safety (types and incidence of AEs) is further defined in a specific patient population/ disease setting.

Overall, sufficient evidence should be generated to support the phase III development of the compound. As part of the strategic development, the phase II trial sets the course for the conduct of the phase III trial in a certain disease or, in case of negative results, demonstrates its futility.

Types of phase II studies

Phase II studies can be investigator-initiated or based on co-operative group efforts. They are conducted in the light of a clinically driven rationale/ unmet need and usually evaluate single agents or combinations with existing therapies. The consensus recommendations on the design of phase II clinical trials testing cancer therapeutics by the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee details several types of phase II trials (**Figure 1**) [5].
In clinical practice, single-arm versus randomized studies have been used as the primary categorization. Single-arm studies include a smaller sample size and a one-stage or two-stage design. They are conducted with the expectation of certain response rates based on historical information or control databases. Randomized trials, on the other hand, are generally larger and ideal for the comparison of a primary endpoint or for "calibration" against a control arm, where expected outcomes are less certain. They can have a comparative or non-comparative design. Randomized trials are more expensive than single-arm studies, but offer the advantage of exploring multiple arms at once.
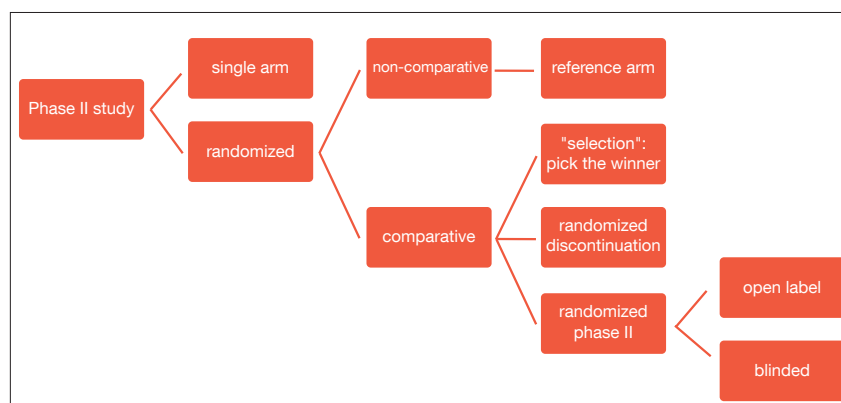

Figure 1: Types of phase II studies

Population selection

It is important to include patients who are most likely to benefit from the intervention being tested. Those who are unlikely to benefit or who show a greater risk of harm should be excluded. Overall, a homogeneous population should be strived for. Selection can be driven by a priori information or clinical factors. A priori information relates to knowledge on the disease prevalence of a particular protein or gene abnormality that predicts for a greater benefit based on the mode of action of a specific drug (biological rationale); also, existent pre-clinical evidence for activity of a drug/ proof of concept in a distinct tumor type might be decisive. Clinical factors include responses observed in the phase I setting, or the biological rationale in a disease area of unmet need.

Population enrichment follows a two-stage design [6]. The learn phase comprises determination of the biomarker status and comparison of the study drug with the comparator using two cohorts that consist of biomarker-positive and biomarker-negative patients. In the confirm phase, the study drug is tested against the comparator in the biomarker-positive population only, if a clear trend of superior efficacy versus the biomarker-negative cohort has been demonstrated. If similar treatment effects occurred in both cohorts, the entire population can be carried forward.

Pertinent endpoints

A number of study endpoints to choose among has been defined (**Table 5**). For primary endpoint selection, the decision between response rates (RR) and progression-free survival (PFS) requires understanding of the expected drug effects on the disease (e. g., cytotoxic versus cytostatic activity, first line versus second

TABLE 5
Trial endpoints
Response rate (RR)*
Progression-free survival (PFS)*
Overall survival (OS)
Patient-reported outcomes (PRO)/ Quality of life (QoL)
Molecular biomarkers, e.g., biomarker expression
Functional imaging, e.g., PET
Toxicity
* On the assumption that these are intermediate predictors for OS

TABLE 6
Characteristics of trials on targeted agents with no clear distinction between the phases I and II

	Phase II/III	Phase III
Purpose	Definition of MTD & activity	Comparison with standard of care
Emphasis	Safety & activity & biomarker	Efficacy
Endpoint	Toxicity & response (all and selected) & preliminary survival	Survival (PFS, OS)
Patients (n)	100-1,000	200-2,000
Registration value	Real (conditional, breakthrough)	Major (confirmatory)

MTD, maximum tolerated dose. PFS, progression-free survival. OS, overall survival.

Take home message

Phase II trials aim at assessing the activity of a compound in a given tumor type in a more homogeneous population, while further defining safety. Patient selection can be driven by a priori information or clinical factors. Early-phase trials into targeted therapies often show no clear distinction between phases I and II. Combined data from these phases can be the basis of accelerated approval. Amalgamation is also possible between phase II and III. Another variation of adaptive trial designs relates to the omission of phase II under certain circumstances.

line versus maintenance). The rigor of the choice between RR and PFS according to Response Evaluation Criteria In Solid Tumors (RECIST) depends on the goal of the study, e. g., activity "screening" trial (investigator review) or decision-making "go/ no-go" trial (independent review).

When RR has been selected for a monotherapy trial, a single-arm design is acceptable. Randomization is required for testing of different doses or schedules or for the comparison with other active therapies. For the assessment of combination therapy (e. g., standard therapy with or without a novel agent, or combinations of novel agents), a randomized design is usually preferred.

Adaptive trial designs

With the dawning of the era of targeted treatments, the differences between the classical phases of drug development have increasingly become blurred. In the early stage, there is often no clear distinction between phases I and II (**Table 6**).

This amalgamation is enhanced by the possibility of accelerated approval, which is usually based on combined data from these two phases. After conditional approval has been granted by the authorities, a phase III study needs to be conducted as a confirmatory trial for full approval.

Adaptive designs also include intermixture of phases II and III. The design presented in **Figure 2** shows a trial evaluating two experimental drugs alone and in combination [7]. After the single agent (drug B) has been selected in phase II, it continues into phase III. The number of patients and the randomization in phase II are chosen adaptively, and phase II results determine the sample size in phase III. Interim analyses might be used to halt phase III early on, either for futility or for expected success. There is also the possibility of omitting phase II: when the design of the phases I and II clearly answers the key questions on safety and efficacy, regulatory authorities now even consider a direct transition to phase III. ■
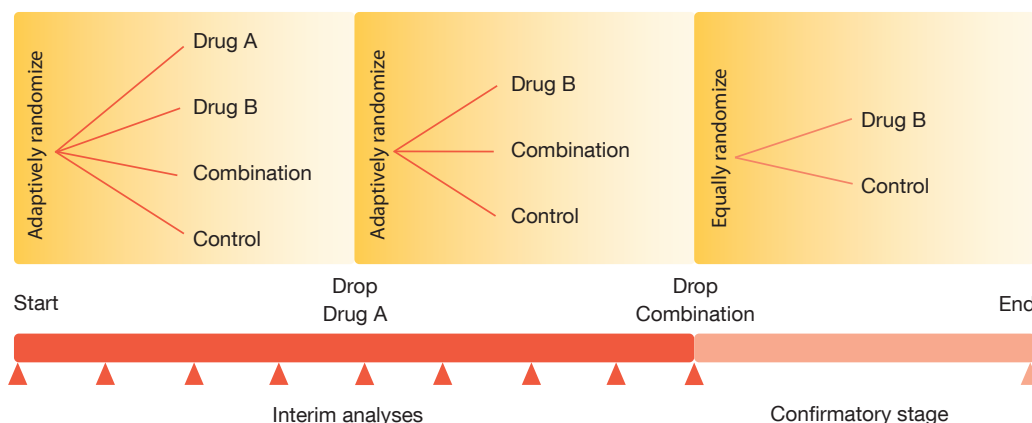

Figure 2: Example of a seamless phase II-III design

James Yang

Clinical trial endpoint selection

Endpoint selection is a crucial aspect in the context of clinical trial design. The investigated outcomes should be clinically relevant, reliable, sensitive and specific, among others (**Table 7**). Legal requirements characterize the primary endpoint as a valid and reliable measure that provides the most clinically relevant and convincing evidence.

Definitions

Commonly used endpoints are based on survival, tumor response, and symptom assessment. Historically, overall survival (OS) has been viewed as the most effective measure as it addresses the biology of the tumor and the natural history of disease. PFS possesses significance because it assesses tumor shrinkage and stabilization of disease. Response rates enable objective demonstration of the drug effect; also, durability of response is taken into consideration. From the patient point of view, symptom assessment is one of the most important endpoints.

Phase III or confirmatory studies call for OS as the primary endpoint. PFS is possible where clinically relevant and can be regarded as a surrogate of OS when OS differences cannot be achieved due to crossover. RR is not recommended as the primary endpoint in this setting. For accelerated approval, the results must predict the clinical benefit of the new drug/ combination over the available therapy. Here, overall RR and response duration have been the most commonly used surrogate endpoints. PFS is also acceptable under some conditions.

In the phase III setting, the absolute magnitude of the treatment benefit needs to be taken into account when judging the activity of a certain regimen. Large numbers of recruited patients can render the differences between the study drug and the comparator statistically significant, but this does not automatically imply clinical significance. However, randomized controlled trials only require large sample sizes when the goal is the identification of small treatment effects.

Generally, the selected endpoints should be reflective of patient benefit; therefore, it is commendable to use OS, PFS and some assessment of symptom relief or quality of life. **Table 8** specifies key guidelines for clinical trial endpoint selection.

Overall survival

OS is accepted as the gold standard for the evaluation of oncological agents. It is objective, easily measureable, clinically significant, accurate, not prone to investigator or assessment bias, and readily comparable across diseases.8 If OS is used as a secondary endpoint, the trial should be powered sufficiently for the assessment of this outcome.

Several drawbacks of OS prevent its use in many trials, however. OS requires long observational periods and large sample sizes; it is influenced by post-trial therapy and complex to analyze when many salvage agents have been administered after completion of the study. Overall, this endpoint makes trial conduct comparatively expensive. Challenges on the statistical level comprise the magnitude of the benefit, the impact of further treatment, and the role of crossover (**Table 9**). Hazard ratios of 0.7–0.8 are recommended, and a median OS benefit of 2–3 months is thought to be clinically meaningful.

According to the ASCO Consensus, which emphasizes the use of OS as an endpoint, clinical trials should aim to improve OS by at least 25 % [9]. The Consensus states that agents not expected to provide such an OS gain would no longer be needed in clinical practice. However, this threshold was arbitrarily defined and is rather difficult to achieve for many large phase III clinical trials. The same guideline refers to exceptions in certain clinical situations, such as the emergence of secondary

TABLE 8

Key guidelines for clinical trial endpoint selection

The decision should always be related to
- the patient subpopulation of interest, as a greater magnitude of effect can be expected in a cohort that has been selected based on tumor biology/ mode of action of the investigational drug
- the stage of disease depending on the type of cancer
- the characteristics of the treatment (toxicity, efficacy)
- the aims of the trial (superiority/ non-inferiority/ safety)
- other treatments already available to that group of patients
- ethics
- practical feasibility (e.g., costs, logistics)

TABLE 7

Characteristics of clinical endpoints

Characteristic	Meaning
Relevant	Clinically important/ useful
Quantifiable	Measured on an appropriate scale
Valid	Measures the intended effect
Objective	Interpreted effect yields consistent measurements
Reliable	Same effect yields consistent measurements
Sensitive	Response to small changes in effect
Specific	Unaffected by extraneous influences
Precise	Small variability
Other	Tradition, cost, time…

TABLE 9		
Challenges in the context of using OS as an endpoint		
Magnitude of the benefit	**Impact of further treatment (post-study therapy)**	**Role of crossover**
Hazard ratio of 0.7-0.8 is recommended	Cannot be excluded	Is it indeed unethical to avoid crossover?
Median benefit of 2-3 months is thought to be clinically meaningful	Treatment lines beyond first line have fewer benefits	
Should be realistic and achievable in the development of new drugs	No major imbalances in subsequent treatments among the arms in large phase III trials	

driver mutations after progression during first-line targeted therapies. Success can be obtained with second-line treatment in these patients, but this makes OS difficult to assess. The use of PFS as a clinically meaningful endpoint can be appropriate here. PFS has been employed for the clinical assessment of many targeted drugs approved in non-small-cell lung cancer. However, OS continues to be an important endpoint, as for example the proof of OS gains through the addition of particular drugs to chemotherapy can be indispensable.

Progression-free survival

Surrogate markers offer several advantages. They can be measured earlier, more frequently and in a more convenient or less invasive way than established markers. Also, reductions in the size of clinical trials and shortening of trial duration are rendered possible, which results in acceleration of the approval process. PFS is widely used as a surrogate endpoint for OS in trials on targeted agents. Compared to OS, it is less influenced by competing causes of death or post-progression therapy. Progression events occur early and more frequently than death events, which optimizes assessment. The oncological community harbors the growing belief that delaying progression in metastatic disease is worthwhile, even if OS is not improved. From the patient point of view, PFS has become an important outcome due to the psychological significance of disease progression and its implications for quality of life. Accordingly, the number of studies using PFS as an endpoint has increased by a massive amount over the last decades [10].

On the other hand, PFS can be affected by assessment bias (investigators declare patients in the control arm progressors to get them on the active experimental therapy as soon as possible), evolution-time bias (suspected progression may be formally evaluated later in one arm than in the other), and attrition bias (more patients withdraw from one arm than from the other). Also, the exact time of progression tends to be unknown, as this depends on the frequency of radiological assessment. If imaging is performed every 3 months, a given patient can have been progressive for 2 months already at the time of the next assessment after he had been declared progression-free at the last one.

Moreover, clinical progression (e.g., weight loss, increases in symptom burden) without any visible increases in tumor size can occur. Assessment bias is the reason why independent review has become a certain standard to verify measurements.

Overall, PFS is challenging to employ as a regulatory endpoint, but it will continue to have a future role in oncology drug registration if rigorous acceptance criteria and standards are met. There will be increasing regulatory pressure to link or associate PFS benefits with other clinical trial outcomes that show direct clinical benefit (e.g. quality of life benefits, disease-related symptom benefits, positive OS trends). PFS might have its best future applications in symptomatic disease and/ or in settings where delay in disease progression correlates with delay in symptom onset. ∎

Take home message

Trial endpoints are based on survival, tumor response, and symptom assessment. Even though OS is accepted as the gold standard for the evaluation of oncology agents, especially in phase III trials, it has several disadvantages such as the necessity for long observation periods and large sample sizes. PFS is widely used as a surrogate endpoint for OS in trials on targeted agents, but a number of biases need to be taken into account when analyzing PFS results. Generally, the selected endpoints should reflect patient benefit (e.g., OS, PFS, quality of life).

Silvia Novello

Quality of life as an endpoint

Quality of life (QoL) assessment adds useful information to the efficacy and safety data obtained in clinical studies. It contributes to the evaluation of different treatments and identifies patients who might benefit from supportive interventions. QoL data can be used to inform policy and resource allocation, reveal benefits to patients despite objective toxicity, and be of prognostic value. Evaluation of patient's QoL might help to determine the suitable moment to start specific palliative interventions.

Patient numbers and patient compliance is an important factor; if they are not substantial at baseline, no reliable results can expected later on, as

compliance tends to decrease over the course of the study. This is of particular significance with regard to long-term treatments like targeted therapies or immunotherapies.

Guidelines have introduced QoL as one factor to define the best treatment. Consequently, almost all of the clinical studies conducted today with the aim of evaluating a new treatment include one or two QoL assessments, and this has increased substantially over the last decades. QoL questionnaires are usually administered in conjunction with response evaluation. Outside of clinical trials, a single assessment can already be helpful.

Overall, the aspect of QoL is of great importance, as the impact of a malignant disease on a person's life matters in the popular perception. This is reflected by a multitude of movies that deal with the topic of cancer.

Obstacles to QoL evaluation

However, in clinical practice, physicians frequently fail to assess QoL. They often feel that clinical judgement is sufficient and that testing takes too much time. Furthermore, they do not know which test to use and how to analyse and interpret it. An enormous range of QoL assessment instruments has cropped up over time. Also, a common perception is the assumption that the patients will get upset when being confronted with QoL assessments. Frequently it cannot be controlled whether the patient themselves or another person who has a different perception of the disease actually fills in the questionnaire. Trained nurses who hand out the questionnaires and explain about them to the patients might be helpful here. Translation can be another issue, as many questionnaires are being distributed to patients around the globe using "literal translation" without taking into account different cultures, attitudes and nuances of language.

On the level of clinical trials, the main challenge resulting from QoL evaluation is the drawing of conclusions, as several factors including the use of questionnaires, methods of data collection and data read-out differ between studies. Even if a substantial amount of data is available, these disparities impede the creation of generally valid statements.

Assessment tools

Overall, generic measurements (assessment of QoL with the same treatment in different diseases) are distinguished from specific ones (e.g., the Lung Cancer Symptom Scale [LCSS]). The decision which one to go for in a given case can be difficult. It appears sensible to use both generic and specific assessment tools, as this allows for a comprehensive evaluation of the patient.

The EQ-5D is a generic measure of health status for patients with various diseases. It encompasses five dimensions (anxiety/ depression, mobility, pain/ discomfort, usual activities, self-care) (**Figure 3**). A patient's overall health status is measured on a visual analog scale (VAS), which is easy to use. VAS use reduces the time of filling in questionnaires and can take place throughout the entire disease process until a patient's death. Another example of a visual scale is the Edmonton Symptom Assessment System. It provides a rapid and simple assessment of symptom intensity, both in routine practice and in the context of research trials. Nine major symptoms (pain, nausea, tiredness etc.) have been defined.

The EORTC QLQ-C30 questionnaire was developed to assess QoL in cancer patients in general. It consists of five functional scales, three symptom scales, one global health status scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). Supplemental disease-specific modules are available for a range of distinct cancer types, as are many other generic instruments.

Lung-cancer-specific questionnaires

The EORTC QLQ-L13, which has been designed for lung cancer patients, incorporates one multi-item scale to assess dyspnea and a series of single items investigating cough, pain, sore mouth, dysphagia, peripheral neuropathy, alopecia, and use of pain medication. A recent update of the EORTC QLQ-L13 was established based on the results of an international, multi-center, phase III study [11]. The new module named EORTC QLQ-LC29 retains 12 of the 13 original LC13 items and includes new items that assess

Figure 3: The EQ-5D Utility Index questionnaire

FACT-L

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the** past 7 days.

	Not at all	A little bit	Some-what	Quite a bit	Very much
PHYSICAL WELL-BEING					
EMOTIONAL WELL-BEING					
ADDITIONAL CONCERNS					

I have been short of breath 0 1 2 3 4

Have you ever smoked?
No ___ Yes ___ If yes:

I regret my smoking 0 1 2 3 4

Figure 4: Design of the FACT-L questionnaire

side effects of targeted therapy, radio-chemotherapy, and thoracic surgery.

Likewise, FACT-L is specific for lung cancer. It comprises 36 questions and 5 domains and assesses physical, functional, emotional and social items, as well as pulmonary symptoms. Unlike other questionnaires, it contains a question as to whether the patient regrets smoking (**Figure 4**).

Methods of administration

QoL evaluation can be performed in the setting of face-to-face interviews by trained interviewers, by telephone interviews, or by use of self-report questionnaires. Data collection is possible via both pencil and paper questionnaires and electronic instruments.

Naturally, elderly patients tend to have problems handling computers, but publications such as a study comparing the LCSS paper form with its electronic version (eLCSS-QL) revealed high acceptance [12]. Eighty-seven percent of patients required less than 3 minutes to learn how to use the electronic questionnaire. Good compliance was observed in the vast majority of cases, as well as reductions in the time of filling in the questionnaire. Also, the majority of the physicians and nurses involved in the study found all aspects of the eLCSS-QL easy to use and interpret. Application of the eLCSS-QL contributed to improvements with respect to the measurement of score ratings, collation of data for analysis, and maintenance of patient confidentiality thanks to the use of passwords. As no transcription of data is necessary, mistakes are avoided.

Patient-reported outcomes

Any outcome evaluated directly by the patient himself that is based on the patient perception of a disease and its treatment(s) is called patient-reported outcome (PRO) [13]. The term PRO has been proposed as an umbrella term to cover both single-dimension and multi-dimension measures relating to symptoms, health-related quality of life, health status, adherence to treatment, and satisfaction with treatment. PROs are of practical relevance because the patient and physician perceptions of various aspects such as the usefulness or toxicity of a certain treatment can deviate from each other to a considerable degree [14–16]. While physicians might rate a small OS advantage negligible, patients would accept chemotherapy if it substantially reduced symptoms even without prolonging life [14]. Expectations of therapy and AEs are important determinants for patient compliance [17].

In a tumor type such as lung cancer that is accompanied by debilitating physical and psychological symptoms, the study of symptom clusters is relevant to identify primary and secondary symptoms and to define their role for patient QoL. This approach can potentially improve the comprehensive QoL management in lung cancer patients. For instance, fatigue is particularly common and severe in lung cancer, reducing QoL in 57–100 % of patients from diagnosis to death [18]. The ASCO guidelines therefore recommend screening for fatigue in daily practice from the time of diagnosis, even if no questionnaires are routinely used [19]. ∎

Take home message

QoL has become an accepted endpoint in oncology trials, and QoL assessment is part of almost all of the clinical studies on new treatments conducted today. Generic questionnaires are available for a range of diseases, while specific questionnaires such as the EORTC QLQ-L13 or FACT-L focus on certain tumor types. Electronic QoL assessment can be expected to meet high acceptance and to simplify the process. PROs represent an important parameter, as patient and physician perceptions tend to deviate from each other to a considerable degree.

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