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Efficacy Endpoints in Adjuvant and Neoadjuvant Oncology Trials

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ABSTRACT

Depending on the type, location, and grade of cancer, different combinations of disease therapy exist. Each particular case requires a special approach for analysis. For instance, RECIST 1.1 criteria remain the gold-standard outcome measure for solid tumors when the investigator assesses the anatomical tumor burden and its change in the study follow-up. However, for study designs where there are different combinations of Adjuvant and Neoadjuvant treatments coupled with cancer surgery, pure RECIST 1.1 could be not as indicative. For such cases, alternative endpoints might help to predict a clinical benefit to the patient and allow to reduce the trial duration. Pathological complete response (pCR) and time-to-event end-points such as disease-free survival are frequently incorporated into pivotal clinical trials in neoadjuvant and adjuvant settings. The purpose of this paper is to introduce key concepts, study designs, and specific efficacy endpoints in Adjuvant/Neoadjuvant Oncology.

INTRODUCTION

Accurate evaluations of the response to neoadjuvant and adjuvant therapies provide important information on the impact of systemic therapies on the particular cancer biology, prognosis, and guidance for further therapy. In clinical trial design, an endpoint is a predetermined outcome that is used to measure the effectiveness of a new treatment or intervention being tested. Due to the limitations of patient-oriented endpoints (such as OS and QoL) evaluation development and validation of new surrogate endpoints are essential.

This review explores the main surrogate endpoints that are commonly used in clinical studies and which of them are suitable for adjuvant and neoadjuvant therapies. Also, we would like to focus on using the pathological response and investigate if this measurement could serve as a valuable surrogate prognostic factor of survival after therapy.

CLINICAL TRIALS FOR ADJUVANT/NEOADJUVANT ONCOLOGY. VARIOUS METHODS OF INFLUENCING THE TUMOR

Simplifying the classification of oncology clinical trials, all cancer clinical trials can be divided into surgical and non-surgical trials (for operable and advanced or metastatic cancer respectively). Non-surgical studies usually consist of three main phases: screening, the protocol treatment phase, and the follow-up phase (see Picture 1).

Picture 1. Clinical trial schema without surgery

Clinical trials that involve the sequencing of surgery and anti-cancer treatments, such as chemotherapy, radiation therapy, or targeted therapies can also be divided into several types such as:

- Neoadjuvant
- Adjuvant
- Perioperative.

NEOADJUVANT CLINICAL TRIALS

Neoadjuvant clinical trials are research studies that investigate the effectiveness of treatments given prior to the main treatment, which is usually surgery, for cancer. The term "neoadjuvant" refers to interventions administered before the main treatment to achieve specific goals, such as reducing the tumor size, enhancing the response to subsequent treatment, or facilitating surgical removal. The aim of neoadjuvant therapy is to enhance the outcomes of primary treatment by preparing the tumor for surgical removal or making it more responsive to subsequent therapies. Common treatments involved in these trials include chemotherapy, targeted therapy, or immunotherapy administered before the surgery. The objective is to assess the tumor's response to the treatment and reduce its size, which can improve surgical outcomes and the overall survival of the patient. The main phases of neoadjuvant studies are displayed in Picture 2.

Picture 2. Clinical trial schema with neoadjuvant treatment

Neoadjuvant therapy has many potential advantages. First of all, neoadjuvant therapy can eliminate all the micrometastasis to the greatest extent, thereby increasing the chance of survival. Secondly, the pathological changes after the resection provide a reliable method for evaluating the impact of neoadjuvant therapy on tumors. At least in principle, the detection of the residual tumors provides an opportunity to change (when the response is considered suboptimal) or continue (when the treatment has shown good activity) the induction program after surgery. Thirdly, the tissues obtained before and after the treatment can be used for translational research and utilization of alternative endpoints, thereby significantly speeding up the translation of clinical research results into the drug approval.

ADJUVANT CLINICAL TRIALS

Adjuvant trials investigate the efficacy of treatments given after the initial cancer treatment, which often involves surgery to remove the primary tumor. Adjuvant trials evaluate whether additional treatments, such as chemo, radiation therapy, targeted therapy, or immunotherapy, can effectively reduce the risk of cancer recurrence after removing the primary tumor. Adjuvant therapy aims to eliminate any cancer cells that remain undetected after the primary tumor removal and could result in recurrence. Adjuvant clinical trials determine whether additional treatments can improve disease-free survival and overall survival rates for patients. These trials are essential for shaping the treatment guidelines and improving long-term outcomes for individuals who have undergone a surgical tumor removal (see Picture 3).

Picture 3. Clinical trial schema with adjuvant treatment

Also, perioperative methods exist where both Neoadjuvant (before) and Adjuvant (after) phases are included (see Picture 4):

Picture 4. Clinical trial schema with both neoadjuvant and adjuvant treatment

Surgical removal of the primary tumor remains a fundamental curative approach in both adjuvant and neoadjuvant clinical trials. The goal of surgery is to remove as much of the tumor as possible, potentially eradicating all the cancerous tissue. To increase the chances of a successful outcome by addressing any residual disease, reducing the risk of recurrence, and improving long-term survival rates, adjuvant and neoadjuvant therapies are used alongside the surgery.

EFFICACY ENDPOINTS IN THE ONCOLOGY CLINICAL TRIALS

The aim of each clinical trial is to prove or refute the effectiveness of the particular therapy. A clinical endpoint is an objective tool used to measure how beneficial a medical intervention is to a patient's feeling, function, and survival. Clinical endpoints are used in clinical trials to assess the validity and generalizability of the study, and the evidence they generate is important to clinicians and patients alike.

Primary or secondary endpoints in oncologic clinical trials can be classified into two main categories: "patient-centered clinical endpoints" including overall survival (OS) and health-related quality of life (QoL), and "tumor-centered clinical endpoints" such as disease-free survival (DFS) and progression-free survival (PFS).

PATIENT-CENTERED CLINICAL ENDPOINTS

Patient-centered clinical endpoints are variables that reflect a patient's feeling of well-being or his/her survival. They assess the effects of a therapeutic intervention for the patients in clinical trials and evaluate the direct patient clinical benefit.

OVERALL SURVIVAL

Overall survival (OS) is defined as the time from randomization to death. Any patients lost to follow up or still alive at the time of evaluation are censored. Since the goal of cancer treatment is generally to extend survival, OS is often referred to as the gold standard endpoint in oncology clinical trials. OS is a patient-centered endpoint that is easy to measure; it is definite since the final time point is death. Moreover, OS is objective, and researcher's bias is unlikely to take place.

The US Food and Drug Administration (FDA) has considered OS as a universally accepted measure of direct treatment benefit and the preferred endpoint of Phase III clinical trials.

While OS remains the preferred clinical endpoint in oncology clinical trials, it has some drawbacks. Primarily, the expectation of a long-term patient follow-up indicates that a larger patient population is required and the study will require more financial support. Additionally, OS has limited use in diseases that are slowly progressing and have an expected long-term survival. In these cases, OS may be influenced by the treatment in further steps, sequential use of other agents, and cross-over treatments, making it difficult to attribute the clinical endpoint to a specific medical intervention. Additionally, as a primary clinical endpoint, OS can also be influenced by non-cancer deaths since the endpoint is defined as time from randomization to death of any cause.

HEALTH-RELATED QUALITY OF LIFE (QOL)

QoL reflects direct clinical benefit of treatments for the patient. The goal of including HRQoL as a clinical endpoint is to complete the results quantitative endpoints such as OS. Quality of life is often used as a secondary clinical endpoint to compare treatments that have similar effects with differences in toxicity, but it can also be used as a co-primary endpoint with OS. HRQoL is usually assessed through the use of a set of four core questions developed by the Centers for Disease Control and Prevention (CDC). The four core questions include concepts related to overall health, physical health, mental health, and activities of daily living, and they can also be supplemented by different modules for specific cancer types.

Opponents of QoL as a primary endpoint note its limitations due to its subjective nature, the lack of standardization for analyzing and reporting QoL results, and incomplete data, as patient assessments can be missed at specified time points as a consequence of skipped visits or failure to complete prescribed questionnaires.

All these disadvantages of OS and QoL endpoints support the need for surrogate clinical endpoints that could be assessed earlier in the clinical course [1] [2].

TUMOR-CENTERED ENDPOINTS

Tumor-centered endpoints are composite endpoints, based on tumor assessment, and they combine different events such as local and distant progression, local and distant recurrence, development of metachronous cancer, death, or severe toxicity.

Tumor-centered clinical endpoints are used as a substitute for a patient-centered clinical endpoint. In most oncologic clinical trials these endpoints include laboratory or histology markers to define a response to a therapeutic intervention. These endpoints are frequently used by oncologists as primary outcomes in oncologic clinical trials because they are available earlier than OS, are less influenced than OS by competing causes of death, and are not influenced by treatments administered after progression. For instance, tumor response (RECIST), circulating tumor cells, disease-free survival (DFS) and progression-free survival (PFS) are tumor-centered clinical endpoints.

But tumor response may not be an indicative endpoint for those clinical studies where the primary tumor has been surgically removed since in that case there are no detectable tumors to measure. For such scenarios, RECIST criteria are reflecting tumor shrinkage is probably not the most appropriate metric.

For neoadjuvant studies, the response can be assessed and determined by the investigator in accordance with RECIST only before the surgical removal of the tumor. Also RECIST is used to evaluate the disease progression that precludes the surgery.

On the other hand, the strategy of neoadjuvant therapy permits investigators to assess tumor response on a pathological basis. In this setting, it may be possible to assess treatment benefits in a more meaningful way than in traditional trials using RECIST v1.1 [3].

SURROGATE ENDPOINTS FOR ADJUVANT AND NEOADJUVANT THERAPIES

Surrogate endpoints in clinical trials are alternative or indirect measures of a treatment's clinical benefit.

These endpoints are typically easier, quicker, or more practical to measure than the ultimate clinical outcomes of interest, such as overall survival or disease-specific survival. Surrogate endpoints aim to provide insights into a treatment's potential effectiveness. Researchers can use these insights to predict the impacts of the treatment on long-term outcomes without waiting for those outcomes to occur.[4]

The most commonly used efficacy endpoints in adjuvant and neoadjuvant clinical trials are the following [5]:

Endpoint	Summary	Advantages	Disadvantages	Relevance
Overall Survival (OS)	Time from Randomization to Death	The gold standard for measuring efficacy in Oncology	Can require longer and larger clinical studies; Includes noncancer deaths; May be affected by crossover and subsequent therapies	Neoadjuvant; Adjuvant; Advanced and metastatic
Disease-free survival (DFS)	Time from randomization until evidence of disease recurrence. All events are included, except the loss to follow-up	Generally assessed earlier and with a smaller sample size compared with survival studies; Generally based on objective and quantitative assessment	Does not necessarily correlate with survival outcome; Not a good endpoint when comorbidities or tolerability is an issue; Various definitions exist	Adjuvant
Event-free survival (EFS).	Time from randomization to an event which may include disease progression that precludes surgery, local and distant recurrence, discontinuation of the treatment for any reason, or death	A wider range of outcomes that matter to patients' overall quality of life; Reduction of trial duration	Can be complex to interpret, especially if different events have varying degrees of clinical significance; Potential bias in the assessment of treatment effects	Neoadjuvant
Pathological complete response (pCR)	Complete absence of residual viable tumor in the treated tumor bed*	Direct measure of how well the treatment has affected the tumor cells	Correlation with long-term survival should be established; Lack of standardized criteria for evaluating across all cancer types	Neoadjuvant

*The ‘tumor bed’ is defined as the area of a tissue occupied by viable tumor or tumoral regression (necrosis with or without clusters/sheets of pigmented macrophages and fibrosis/fibroinflammatory stroma).

Other endpoints specific to adjuvant clinical trials:

Relapse-free survival (RFS). Time to any event, irrespective of cause, except for any second primary cancers. Recurrence of or death from the same cancer and all treatment-related deaths or deaths from other causes are events. Second primary same cancers and other primary cancers are ignored, and loss to follow-up is censored.

Time to recurrence (TTR). Time to any event related to the same cancer. All the same cancer recurrences and deaths from the same cancer are events. Second primary same cancers and other primary cancers are ignored. Deaths from other cancers, non–cancer-related deaths, treatment-related deaths, and loss to follow-up are censored observations.

Time to treatment failure (TTF). Time to any event, except non-cancer-related death. All recurrences, treatment-related deaths, second same or other primary cancers, and deaths from other cancers are considered to be events. Loss to follow-up and non–non-cancer-related deaths are censored.

Cancer-specific survival (CSS). Time to death is caused by the same cancer, whether due to the original tumor or to a second primary same cancer. The only event is death from the same cancer, without taking into account whether the death is caused by the primary tumor or a second same cancer. Locoregional recurrence, distant metastases, second primary same cancers, and second other primary cancers are ignored. Deaths from other cancers, non–cancer-related deaths, treatment-related deaths, and loss to follow-up are censored.

The summary of the surrogate endpoints and the corresponding occurrences are listed in the table below:

	Endpoints					
Event	DFS	RFS	TTR	TTF	CSS	OS
Locoregional recurrence	E	E	E	E	I	I
Distant metastases	E	E	E	E	I	I
Second primary, same cancer	E	I	I	E	I	I
Second primary, other cancer	E	I	I	E	I	I
Death from the same cancer	E	E	E	E	E	E
Death from other cancer	E	E	C	E	C	E
Non–cancer-related death	E	E	C	C	C	E
Treatment-related death	E	E	C	E	C	E
Loss to follow-up	C	C	C	C	C	C

E = event; C = censor; I = ignore.

OTHER EFFICACY ENDPOINTS SPECIFIC TO NEOADJUVANT TRIALS

Pathological complete response (pCR). Pathological complete response (pCR) in clinical trials is defined as no viable cancer cells left in tumors after treatment.

Major pathological response (MPR). MPR is defined as less than 10% residual viable tumor after neoadjuvant therapy. MPR can be observed more frequently than a pathological complete response (pCR), defined as no viable residual tumor. The 10% cutoff is determined based on the previous studies of the pathological assessment of the resected tumor tissue after neoadjuvant chemoradiotherapy.

Downstaging (DS). The proportion of participants downstaged. Downstaging refers to the reduction in tumor size, extent, or characteristics due to pre-treatment (neoadjuvant) interventions, with the goal of making the tumor more amenable to subsequent curative treatments.

CHALLENGES IN SURROGATE ENDPOINTS SELECTION AND VALIDATION

Statistical validation of a surrogate endpoint is a difficult but necessary process. While selecting the appropriate endpoints is crucial for the success of a clinical trial, it can be difficult to identify which endpoints are relevant to the disease being studied and clinically meaningful, while also being measurable.

Poor selection of endpoints makes interpretation and implementation of findings difficult or impossible, limits evidence synthesis, and thereby diminishes the value of the research, resulting in wasted use of resources. It is therefore crucial

that the chosen endpoints are meaningful to the clinicians, patients and policymakers who are end-users of the evidence generated by these trials.

A major difficulty for the validation of surrogate endpoints arises from the fact that they must be validated with respect to a specific therapeutic class, for a specific disease, and at a specific stage. It is uncertain if the same surrogacy relationship will be applicable for a different treatment or at another stage of the disease.

Additionally, once the endpoints are chosen, it is essential to define them precisely, including how they will be measured and analyzed. There is no international consensus standard for the definitions, consequently the interpretation of the same “endpoint” is variable in different studies of the same disease. Ambiguity or lack of clarity in endpoint definitions can lead to inconsistent interpretation of data across the study sites, which can affect the trial's validity.

Consequently, surrogate clinical endpoints are often used because they can be assessed earlier, but they do not reflect a direct clinical benefit for the patient. There is a lack of consistency in their definitions, and they have not been systematically validated as surrogate endpoints for OS [1] [6].

PATHOLOGICAL RESPONSE IN NEOADJUVANT CLINICAL TRIALS

Pathological response is an important prognostic factor in the management of neoadjuvant clinical trials. It refers to assessment of changes in a tumor tissue after the patients have received pre-treatment therapies, but before the primary treatment (usually surgery) is administered.

The aim of evaluating a pathological response is to determine the extent to which the neoadjuvant treatments have modified the tumor's characteristics, size, and composition. This data can offer valuable insights into the treatments' potential efficacy in achieving long-term results and guiding future treatment decisions.

A pathological complete response (pCR) in neoadjuvant clinical trials is defined as when there is no detectable evidence of viable cancer cells in the tumor tissue after the patients have received pre-treatment therapies. Essentially, pCR means the tumor has completely disappeared at the microscopic level.

Different types of cancer and treatments may have their own criteria for evaluating pathological response. Here are some examples of how pathological response is evaluated in various oncology indications.

Breast Cancer:

The preferred definition of pathological complete response (pCR) is the absence of residual invasive cancer within both the breast and lymph nodes through hematoxylin and eosin staining of the complete resected breast specimen and all sampled regional lymph nodes. No standard definition of pCR exists across different studies, and the FDA has proposed two different definitions: (1) no invasive and non-invasive residual cancer in the breast and lymph nodes (ypT0 ypN0) and (2) no invasive residual cancer in the breast and lymph nodes irrespective of residual non-invasive disease (ypT0/is ypN0). Despite uncertainty about the exact definition and its prognostic impact on survival, pCR is included in the FDA’s Surrogate Endpoint Table only for breast cancer and is used as an intermediate measure in clinical trials for patients with early-stage breast cancer who have completed the systemic neoadjuvant therapy. For high-risk early-stage breast cancer, pCR has been used as a surrogate endpoint reflective of the treatment effect to support accelerated approval and a surrogate endpoint to support traditional approval [7].

Melanoma:

In the early trials for patients with melanoma, pCR is defined as the complete absence of residual viable tumor. pPR was empirically defined as ≤50% of the tumor bed occupied by viable tumor cells, and pathological non-response (pNR) was defined as >50% of the tumor bed occupied by viable tumor cells. Some neoadjuvant immunotherapy studies have also utilized a category of ‘near pCR/major PR’ that was defined as >0% but ≤10% viable tumor cells. Newer grading systems supporting the scoring of residual viable tumor as a continuous variable have also been proposed. Long-term outcome studies are required to determine the extent to which the pathological response is associated with the improved patient survival in distinct neoadjuvant settings [8].

Gastric:

The Japanese Gastric Cancer Association (JGCA) Criteria are used to assess the pathological response of gastric cancer to neoadjuvant chemotherapy. The categories are as follows:

- Grade 1a (GR1a): Complete Response. In this category, there is a complete disappearance of tumor cells. Only fibrosis, inflammation, or scarring is present in the treated tumor bed.
- Grade 1b (GR1b): Near-Complete Response. In GR1b, a small number of tumor cells might be present, but the predominant findings are fibrosis, inflammation, or scarring.
- Grade 2 (GR2): Partial Response. Grade 2 indicates that both tumor cells and fibrosis or inflammation are present in the treated tumor bed.
- Grade 3 (GR3): Poor Response. In the GR3 category, a significant number of viable tumor cells are still present, and the degree of fibrosis or inflammation is minimal.

These are only several examples of diverse standards used to evaluate pathological response in various oncology indications. The specific standards and classifications implemented can vary, and investigators typically select or adapt them depending on factors such as tumor type, treatment regimen, and study objectives [9].

CORRELATION BETWEEN THE PATHOLOGICAL RESPONSE AND OVERALL SURVIVAL

The correlation between pathological response and longer-term outcomes in trials is dependent on many factors. These include definitions of pathological response, both complete and partial; assessment methods for pathological response at surgery; subtype and prognosis of the particular type of cancer at diagnosis; number of patients recruited; adjuvant treatments; the mechanism of action of the investigational drug; the length of follow-up at the time of reporting; the definitions used in longer-term outcomes analysis; and new adaptive trial designs with additional neoadjuvant treatments [10].

There is a known perception that the pCR is relevant for indications that are treated with neoadjuvant immunotherapy or chemotherapy before resection and is one of the most commonly used surrogate endpoints for such studies [11].

Therefore, a clinical response to neoadjuvant chemotherapy, which is commonly reported, does not always accurately reflect the pathological response: residual tumour is frequent in clinically complete responses, and conversely some complete pathological responses are found in good partial clinical responses.

Questions have been raised over the appropriateness of using pathological endpoints as surrogates for long-term clinical outcomes [12]. It is worth noting that there is no relatively common conclusion in the literature regarding the question if the pCR could serve as a valid surrogate endpoint for OS in neoadjuvant studies. There are a few analyses (commonly meta- or literature-based ones) claiming that pCR for neoadjuvant studies is not an appropriate surrogate for OS (in particular, investigations for rectal cancer [13], breast cancer [14], [15]), but on the other hand there are a number of papers proving that pCR is a valid predictor for OS (for example pooled analysis of immunotherapy trials [16], Bladder Cancer [17], Lung Cancer [18], [19]).

Unfortunately, current neoadjuvant chemotherapy trials are not statistically powered (in terms of numbers) for longer-term outcomes. It is expected that pCR might become a key endpoint in the next 2-5 years for neoadjuvant therapies if the correlation with long-term survival is established [11]. Therefore, further research is needed to effectively quantify the association between pathological responses, such as pCR, and long-term outcomes, including EFS and OS.

ANALYSIS METHODS FOR NEOADJUVANT AND ADJUVANT STUDIES

TIME-TO-EVENT ANALYSIS

The analysis of time-to-event efficacy endpoints typically involves survival analysis methods, as these data involve measuring the time until a specific event occurs (e.g., disease recurrence, death). Survival analysis is essential for evaluating the treatment efficacy, estimating survival probabilities, and comparing different treatment groups. Here are the key steps for analyzing time-to-event data:

- Kaplan-Meier Estimate. Kaplan-Meier survival curves visualize survival probabilities over time for different treatment groups.
- Log-Rank Test. The log-rank test is used to compare survival curves between two or more groups. A significant result suggests that at least one group has a different survival experience.
- Cox Proportional-Hazards Model. The Cox proportional-hazards model is a regression model used to assess the impact of multiple variables (e.g., treatment, patient characteristics) on survival while accounting for censoring. It estimates hazard ratios (HRs), which represent the relative risk of the event occurring in one group compared to another.
- Stratified Analysis. Stratified analysis can be performed to assess whether the treatment effect varies across subgroups (e.g., by age, gender, disease stage). Stratification can help identify patient subgroups that benefit most from the treatment.

Time to Event Summary for Disease-Free Survival, Intent-to-Treat Patients
Protocol: AB123456

Earliest Contributing Event to iDFS	Treatment A (N=XX)	Treatment B (N=XX)
Patients with event (%)	xx (xx.x%)	xx (xx.x%)
Earliest contributing event		
Death	xx	xx
Distant Recurrence	xx	x
Regional Recurrence	xx	xx
Patients without event (%)	xx (xx.x%)	xx (xx.x%)
Time to Event (months)		
Median	xx	xx
95% CI	xx	xx
25% and 75%-ile	xx	xx
Range	x.x - xx.x*	x.x* - xx.x*
Stratified Analysis		
p-value (log-rank)	0.xxxx	
Hazard Ratio	x.xx	
95% CI	(x.xx, x.xx)	
Unstratified Analysis		
p-value (log-rank)	x.xxxx	
Hazard Ratio	x.xx	
95% CI	(x.xx, x.xx)	
3 Year Survival		
Patients remaining at risk	xx	xx
Event Free Rate (%)	xx.xx	xx.xx
95% CI	(xx.xx, xx.xx)	(xx.xx, xx.x)
Difference in Event Free Rate	-x.x	
95% CI	(-x.xx, x.xx)	
p-value (Z-test)	0.xxxx	

* Censored value. ^ Censored and event.
Summaries of IDFS (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.

Table 1. Example of representing results for efficacy time-to-event endpoints.

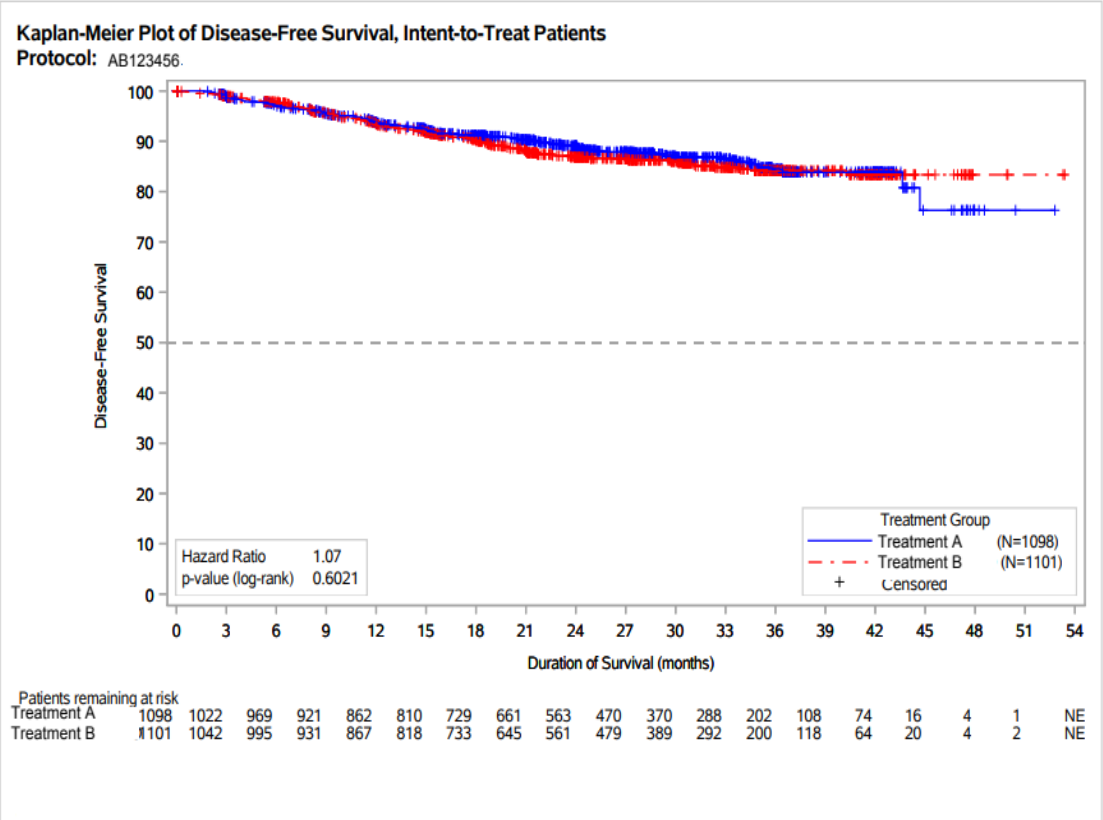


Figure 1. Example of survival curves.

This table and graph are the most common formats for representing time-to-event parameters in clinical trials, in our particular case in clinical trials of adjuvant and neoadjuvant oncology.

ANALYSING OF THE PATHOLOGIC RESPONSE DATA

For the statistical analysis of pathological response well-known waterfall plots can be used as a way of information imaging:

- The waterfall plot by % Area of Non-viable Tumor Bed clearly shows the distribution of evaluated pathological responses (Figure 2):

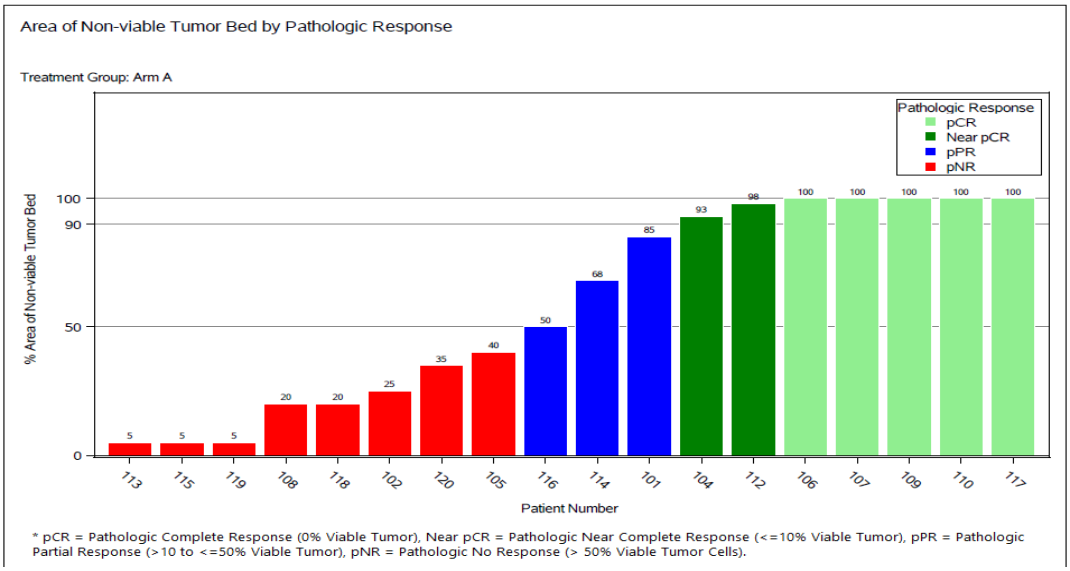


Figure 2. Example of waterfall plot by % Area of Non-viable Tumor Bed by Pathological Response.

- For neoadjuvant studies the combination of both methods of tumor assessment can be used for the better visualisation of response: as we have the assessment of tumor by RECIST v1.1 on screening and before surgery, the best change in the sum of diameters from baseline can be calculated, on the other hand the pathological response is available as well (Figure 3):

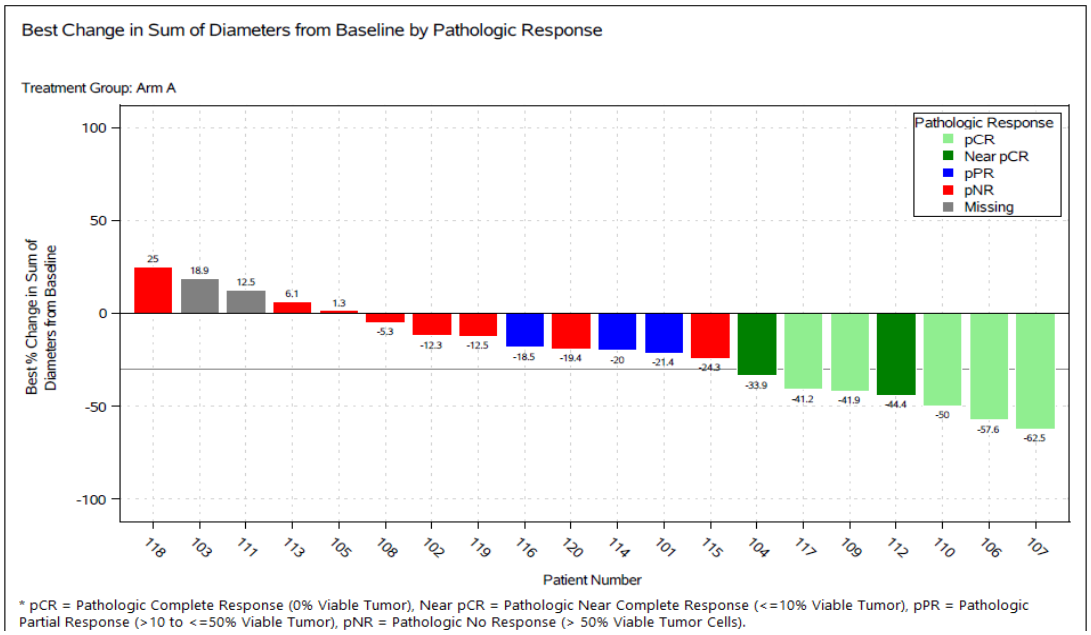


Figure 3. Example of waterfall plot by Best Change in Sum of Diameters from Baseline by Pathological Response.

- Also, pathological response can be analyzed in the context of the area of the tissue occupied by viable tumor and/or evidence of tumoral regression (including necrosis, clusters/sheets of pigmented macrophages, and fibrosis/fibroinflammatory stroma) (Figure 4):

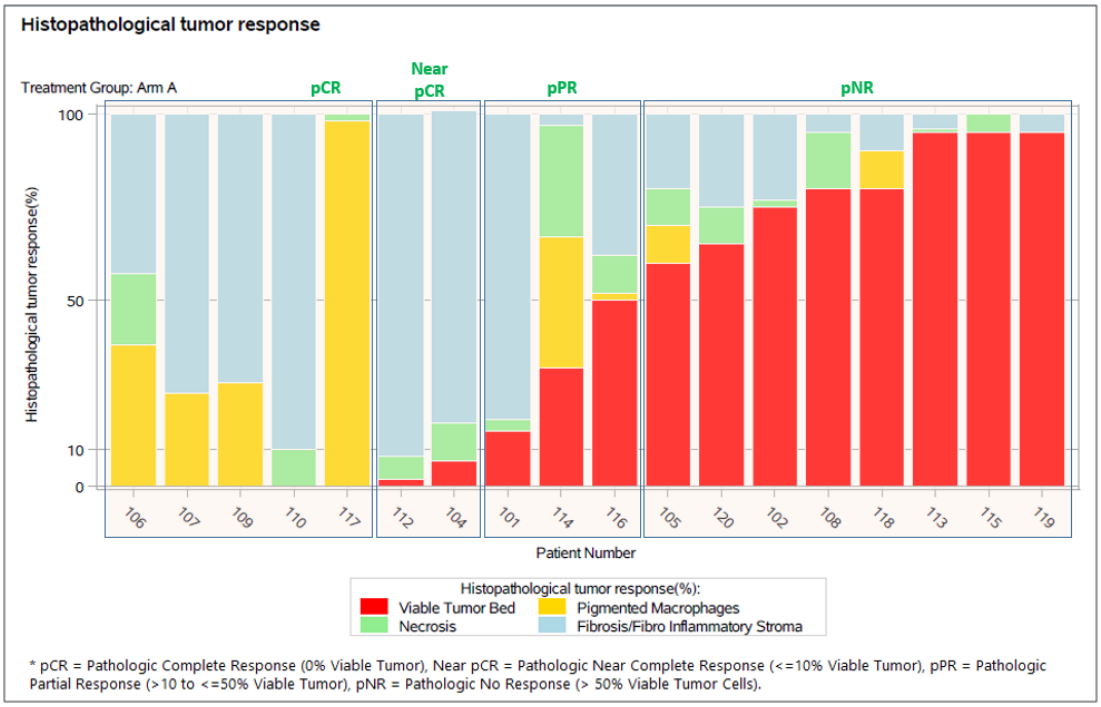


Figure 4. Example of Histopathological tumor response distribution.

- The following layout might be used for the pathological response table (Table 2):

Pathological Response Rates, Intent-to-Treat Patients		
	Arm A (N=xxx)	Arm B (N=xxx)
Pathological Responders	xx (xx.x%)	xx (xx.x%)
95% CI	(xx.xx, xx.xx)	(xx.xx, xx.xx)
Analysis		
Difference in Overall Response Rates (95% CI)	xx.xx (xx.xx, xx.xx)	
Odds Ratio for Overall Response (95% CI)	xx.xx (xx.xx, xx.xx)	
Pathological Complete Response (pCR)	xx (xx.x%)	xx (xx.x%)
95% CI	(xx.xx, xx.xx)	(xx.xx, xx.xx)
Pathological Near Complete Response (Near pCR)	xx (xx.x%)	xx (xx.x%)
95% CI	(xx.xx, xx.xx)	(xx.xx, xx.xx)
Pathological Partial Response (pPR)	xx (xx.x%)	xx (xx.x%)
95% CI	(xx.xx, xx.xx)	(xx.xx, xx.xx)
Pathological No Response (pNR)	xx (xx.x%)	xx (xx.x%)
95% CI	(xx.xx, xx.xx)	(xx.xx, xx.xx)
Missing	xx (xx.x%)	xx (xx.x%)

95% CI for rates were constructed using Clopper-Pearson method. 95% CI for difference in rates were constructed using the Wald method with continuity correction. 95% CI for odds ratio was constructed using the Wald method.

pCR: 0% Viable Tumor, Near pCR: <=10% Viable Tumor, pPR: >10 to <=50% Viable Tumor, pNR: > 50% Viable Tumor Cells.

Table 2. Typical table layout for the pathological response rates.

Listed examples above are the commonly used formats for representing the pathological response parameters.

RECIST V1.1 vs PATHOLOGICAL RESPONSE

Evaluation by RECIST v1.1, with ORR defined as the proportion of patients who achieved CR or PR, remains one of the efficacy endpoints in the neoadjuvant clinical trials. However, some studies observe that among patients in pCR + major PR group, only a few achieved CR or PR by preoperative clinical evaluation by RECIST v1.1.

It is a common phenomenon for the discordant rates between the pathological and RECIST responses in neoadjuvant therapy. When sufficient cycles of neoadjuvant therapy are completed, many types of tumor necrosis, tissue fibrosis, and inflammatory response contribute to maintaining the tumor bulk, which also causes discrepancy of images and pathology and a certain bias in predicting independently the patient's survival [20].

BAYESIAN APPROACH FOR GATING CRITERIA BASED ON PATHOLOGICAL RESPONSE

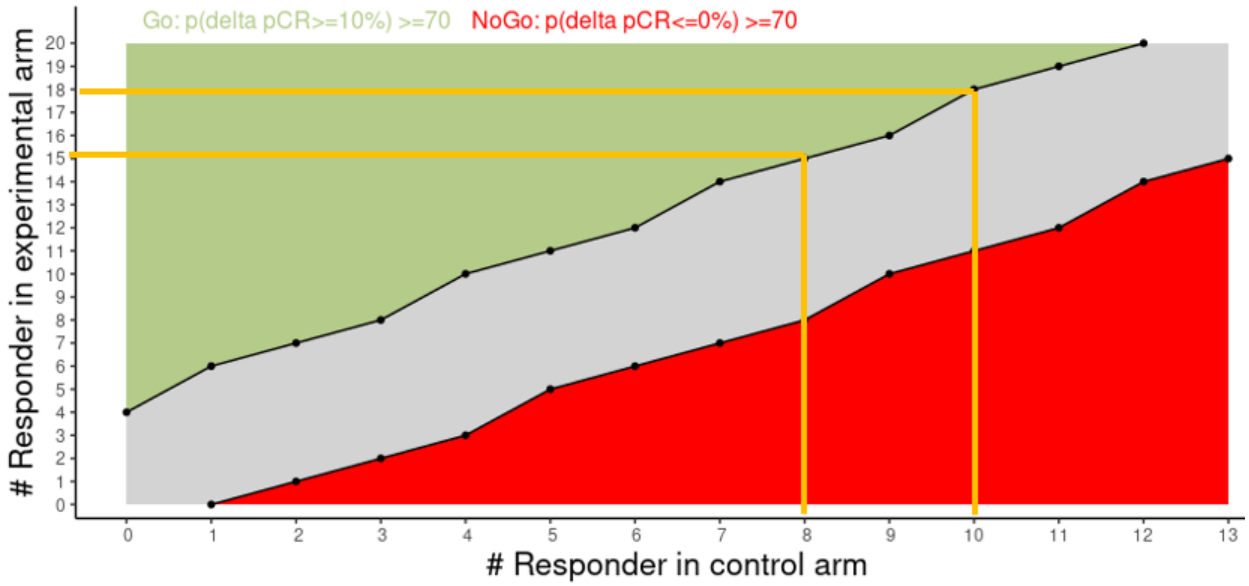
The pathological response results can also be used for the decision making process.

For instance, gating criteria with the use of the Bayesian approach may help to evaluate the potential of the experimental treatment or to decide if it is applicable to expand the existing arm with the experimental treatment and/or open a new arm with the same active treatment (but with a different dosing/frequency, etc.).

Gating criteria should be agreed by group of corresponding specialists, possible values could be as follows:

Decision Parameters	Go for Expansion and Propose Pivotal Trials	Go for Expansion	Evaluate	No-Go
Benefit-risk profile compared to comparator arm (and/or SOC)	Compelling improvement in efficacy Favorable benefit-risk	Promising improvement in efficacy Favorable benefit-risk	Moderate to small improvement in efficacy Favorable benefit-risk	No improvement in efficacy Unfavorable benefit-risk
Primary endpoint of pCR	Bayesian gating P[Δ pCR ≥ x%] ≥ y%, (demonstrative example below, each indication need a specific gating)			
	Prob[ΔpCR ≥ 20%] ≥ 70%	Prob[ΔpCR ≥ 10%] ≥ 70%	Prob(Δ pCR ≥ 10%) < 70% and Prob(Δ pCR ≤ 0%) < 70%	Prob[ΔpCR < 0%] ≥ 70%

For instance, assuming that there will be 20 patients in the active arm and 15 patients in the control arm, the following options are possible:



1) If 8 responders (pCR 53%) are seen in the control arm, the expansion phase would be ungated if 15 responders (pCR 75%) or more would be seen in the exp arm.
2) If 10 responders (pCR 67%) are seen in the control arm, the expansion phase would be ungated if 18 responders (pCR 90%) or more would be seen in the exp arm.
3) If 13 (pCR 87%) or more responders are seen in the control arm, then the expansion decision needs to be evaluated if 16 responders (pCR 80%) or more would be seen in the exp arm.

Therefore, using such approach, the following scenario can appear:

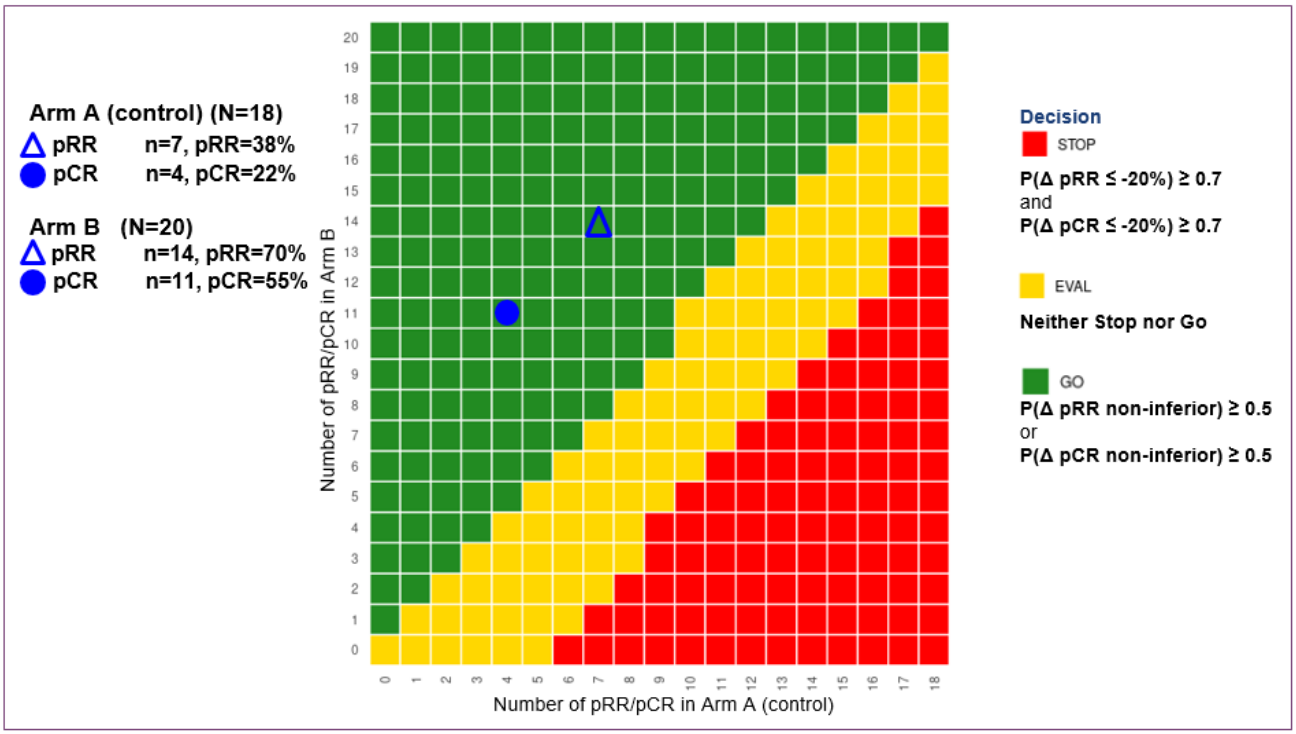


Figure 5. Example of Gating Criteria Using Bayesian Approach visualization.

In this example, the decision to expand the active arm might be made.

POTENTIAL IMPACT OF SURGERY DELAY IN NEOADJUVANT STUDIES

Timely conduct of surgery is an indicator of treatment tolerability. One of the potential issues in the neoadjuvant studies could be the surgery delay compared to the protocol planned date. The neoadjuvant treatment postpones a resection owing to the screening procedures, the preoperative treatment, and the treatment-related adverse events. Optimal timing of the surgery, in terms of OS, disease-free survival (DFS), and perioperative morbidity remains unknown and depends on the type of cancer. Rate and duration of the delayed surgery due to treatment-related adverse events could be used as a safety endpoint.

It is suspected that a delayed surgery after neoadjuvant chemotherapy leads to a worse outcome. There are several survival analyses revealing that long surgery delays increased mortality compared with short delays in resectable NSCLC [21], head and neck squamous cell carcinoma [22], rectal cancer [23], breast cancer [24], suggesting the overall oncologic outcome may be influenced by the timing of the surgery after the neoadjuvant treatment.

The reasons for delayed surgeries may be as follows:

- Protocol-related delays and delays related to neoadjuvant treatment. Clinical trial procedures such as randomization to treatment, screening, and workup, number of neoadjuvant treatment cycles and regimens, preneoadjuvant and postneoadjuvant treatment biopsies and radiography can all contribute to delaying resection.
- Adverse Event-Related Delays.
- Disease progression.
- Neoadjuvant therapy toxicity may require time for recovery.

The acceptable duration of the surgery delay is generally fixed by the protocol, and the rate and duration of the delayed surgery due to particular reasons (especially due to treatment-related adverse events) should be summarized for further investigation. The resection delay may have the potential for increased intraoperative complexity and greater intra- and postoperative morbidity and mortality.

CONCLUSION

Efficacy endpoints in adjuvant and neoadjuvant oncology have their advantages and drawbacks. Time-to-event adjuvant efficacy endpoints such as disease-free survival or recurrence-free survival also allow an earlier than OS evaluation of response but the diverse definitions that depend on disease types make the standardization process more complicated and labor-intensive.

The neoadjuvant treatment paradigm allows the antitumor activity of a novel therapy to be determined on a pathological basis at the time of surgery instead of by RECIST. Pathological response in neoadjuvant clinical trials offers some advantages such as being a potential strong surrogate endpoint, objective and quantifiable assessment, early evaluation off the treatment response, and potential for guiding clinical decisions. However, it also has limitations regarding its correlation with long-term outcomes, the variability in definitions, and its dependence on surgeries.

The correlation between the pathological response at surgery after neoadjuvant chemotherapy and longer-term outcomes at an individual patient level remains unclear, there is considerable amount of meta-analysis for or against the statement that pCR could serve as a substantial surrogate endpoint for neoadjuvant clinical studies. To capture informative prognostic data connected to pathological response in such trials, it is crucial to standardize pathological assessment and reporting of tumor response after the therapy.

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