Part III: A Rational Approach to Clinical Research: Interim Analysis

Chapter 5

Investigational Study 4

Rational approaches to clinical trial: Interim Analysis

My research explains a rational approach to clinical trials that incorporates what is learned during the course of a study or development program into how it is completed, without compromising validity or integrity. The components need not be confined to the frequently encountered but unduly narrow vision of enabling changes in a study’s design, valuable and interesting as such changes are. Rather, this method may encompass potential changes in all program-related resources and activities, including changes in logistical, monitoring, and recruitment procedures, and sometimes even personnel and travel requirements. The goal of this method is making better and more timely decisions to allocate all study resources more efficiently, reduce costs and timelines, and better achieve informational goals compared to traditional study and program approaches.

Efficient management is particularly important in activities as complex as clinical research, which involves a range of activities that includes patient recruitment, randomization, supply chain logistics, and flow of information. Additional complexity commonly arises when pharmaceutical studies are conducted at multiple sites, often in different countries, cultures, and languages. Effective management of clinical trials requires continuous monitoring and measurement of numerous activities. The essence of this research is to continuously measure progress in the many aspects of a complex study, learn from such measures, and, based on what is learned, act expeditiously to make changes to improve the remainder of the study and even an entire development program.

On a realistic level, the study not only require the ability to measure outcomes of interest continuously but also to make data and summarized information about those measurements available in a timely manner to different audiences according to study role. This is essential for effective study management. In a clinical context, this means not just continuously tracking trial data collected on case report forms but also generating performance metrics that enable refinements in operations. This learn-as-you-go approach contrasts with the traditional black – box methodology of clinical trials in which data and particularly operational indices are often lacking altogether or available too late to enable study personnel to respond: Clean data are generally not available until after a study is...
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Completed, and study performance metrics such as recruitment rate, reasons for screen failures, and the like are often lacking entirely.

Interest in this approach has mounted as a result of the soaring cost of clinical research and numerous trial failures, including particularly costly and well-publicized failures of major late-stage trials. In addition to greater efficiency, this approach provide a number of appealing advantages, such as a more nuanced view of product performance that may enable earlier strategic decisions about appropriate target populations, earlier warnings about ineffective trials, and a broader view of research programs as continuous, integrated activities rather than a staccato, linear series of separate trials with inevitable delays in between.

Advances in data capture and validation open possibilities for much earlier understanding of study performance and trends. Computational advances stimulated the development of statistical methodology enabling midcourse “looks” at study progress based on data collected to date. The most common example is sequential analyses, which preserve design integrity but inform decisions that improve the course of the study. The simplest result of such an interim analysis is early stopping for futility or continuation of the study. An additional benefit of this approach is enabling a more nuanced perspective into candidate performance, following the realization over time that a simple “yes – no” answer as to a drug’s efficacy is likely an oversimplification. The rational approach maintain the same high standards of scientific integrity and reliability as the standard methodology while dramatically improving operational and economic efficiency and informational breadth, depth, and quality.

This rational approach also allows clinical researchers to employ the same basic management principles as typical modern businesses, using real-time data and analysis to inform decisions that continually optimize operations. This requires continuously updated operational performance metrics; the conventional approach often lacks the real-time data essential to make such metrics available to improve trial management.

Preserving study integrity the ability to perform unbiased clinical evaluations is paramount with all clinical evaluations, including adaptive ones. While commonplace in other industries, managing in response to changing data is fairly new in clinical research because excluding bias has been achieved primarily by denying access to data, including much of the data that would be useful for trial management. Like conventional trials, rational approach still relies on techniques to exclude bias, including blinding. However, this approach also employs additional planning and special operational procedures that prevent
those performing the study from accessing unblinded results data. Only designated individuals have access to the information required to make decisions about specific adjustments during the trial. Firewalls must be incorporated from the outset to ensure that decision makers cannot jeopardize, whether knowingly or not, the study’s scientific integrity. Fortunately, sophisticated computer access control and data encryption techniques provide useful tools for controlling the dissemination of information and potential sources of bias. Developing protocols for this approach demands more attention than conventional planning because multiple scenarios must be considered and specific plans included for addressing each.

The fundamental principles of this research apply not only to the sophisticated and innovative techniques for strategic adaptations but also to many of the activities common to virtually all clinical studies, whether or not they involve strategic adaptations. Implementing efficient data capture, rapid data cleaning, generation of a range of performance metrics, and readiness for informed decision making based on such information can produce dramatic gains in efficiency. For historical reasons, the pharmaceutical industry makes little use of such capabilities today. Nonetheless, there is no reason why the industry should not take advantage of what amount to the same management techniques already used by most contemporary businesses to bring clinical studies into the modern era.

Since the necessary changes for operational adaptations need not affect study or program design, they do not require regulatory approval. Operational adaptations can therefore be implemented immediately, and their benefits are at least as profound as those flowing from strategic adaptations. One clear illustration is a large, complex phase III evaluation of an Alzheimer’s drug candidate, where efficient collection of data and performance metrics enabled the completion of patient enrollment in record time and the closing of the database within 2 weeks of the last patient visit. As a result, this study saved 1.6 years and $32 million in direct costs measured against the sponsor’s internal projections of 5 years and $100 million [7, 2000; this article can be found online at http://www.healthdec.com/media/articles/AnAlzheimersDrugGoesonTrial.pdf].

As previously noted, the same capabilities involved in making such gains in efficiency are required for all types of adaptive studies. In a broader sense, such capabilities represent the application of principles of tight management to the complex realities of clinical studies. Other industries have shown the way. The principle of just-in-time inventory brought new efficiencies to the automobile industry; the same principle, managing operations based
on continuous, real-time information about important business processes, has been widely adopted in manufacturing and other highly competitive industries. While pharmaceutical development is considerably more complex and knowledge based than manufacturing, intelligent management can apply the same general principles to clinical studies while preserving study integrity and validity through careful operational controls and information management, preserving blinding, randomization, and other hallmarks of clinical research. The need for specific measures to exclude the possibility of bias does not, in an age of sophisticated access control systems, require near total ignorance for all study personnel of all study operations until the very end, when it is too late to take advantage of data and performance metrics for effective trial management. The need to remedy major shortcomings in the efficiency of current development practices is evident; so is the availability of methods with the potential to solve current problems and make dramatic, rapid improvements in efficiency.

Surprisingly, one critical requirement for tight study management is frequently overlooked: the timely reporting of performance metrics. Effective management is impossible without timely, accurate information about performance; in clinical studies, achieving tight management through operational adaptations requires the same capabilities as strategic adaptations: rapid data collection from the field, rapid data cleaning, timely analysis and summarization, and, importantly, presentation of information in different forms meaningful to staff performing different functional roles. The study manager, for example, may be centrally interested in knowing why certain sites are enrolling faster than others and will therefore want to track frequency of screen failures and the distribution of different reasons for them. The field monitor may wish to know how to help a site decrease its query rate, allowing her to spend less time in managing minutiae of the study and, thanks to more accurate data collection and the reduced incidence of queries, more time helping sites conduct the study efficiently and achieve database lock faster. The head of R & D may be most interested in the projected dates for completion of enrollment and database lock.

5.1 Different views on Interim Analysis and Stopping Rule

The general approach for the conduct of interim analyses is to relate the patient accrual information to when interim analyses will occur. There are a number of practical and theoretical justifications for the implementation of this approach in clinical trials via a variety of group sequential designs that allow a limited number of planned analyses while maintaining a pre-specified overall Type I error rate and the blind of the study. In this
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approach, the overall Type I error rate is maintained via significance levels for each test.\(^1\) In addition to this statistical approach, it is essential that the integrity of the trial be maintained. With this in mind, it is highly desirable that the conduct of the interim analyses be done by a body independent of the one charged with the day-to-day activities of the clinical trial. Furthermore, the dissemination of the interim analysis results during the trial is to be limited to persons not directly involved in the conduct of the clinical trial.

In some of these cases, the interim analyses were unplanned and the sponsor failed to report these unscheduled interim analyses and/or adjust the analyses results. In some cases, where the interim analyses were planned, the sponsor used stopping rules inappropriately. There were instances where a formal analysis of the efficacy data was done without any consideration for the adjustment of p-values for the final analysis. Some of the reasons given for failure to carry out such adjustments were: it was an operational or administrative interim analysis, it was not planned, the trial was not stopped, and so forth. There is a common concern among statisticians about the tendency to over interpret observed treatment differences in clinical trials subjected to repeated significance testing. This concern is based on the fact that (unadjusted) repeated significance testing of the accumulating data of a clinical trial increases the overall significance level beyond the pre-specified nominal significance level.

- If the difference between two treatment arms is tested at the end of the trial at the 0.05 level, the chance of concluding they are different when, in fact they are not, is 5%.
- If this same trial is tested halfway through, by plan, as well as at the end, the chance at the half way point is also 5%.
- But if we consider the chance of concluding that there is a difference at either time, then the chance is greater than 5%.

(If the first analysis is done not by plan but just because the results look interesting, then the overall chance of concluding that there is difference at either time is much greater than 5%.)

There are a number of prospective statistical strategies for positive stopping (i.e., stopping due to overwhelming evidence of efficacy) of a clinical trial early. The O'Brien-Fleming or Peto-Haybittle\(^1\) guidelines are the most widely used statistical guidelines for this purpose. Another flexible strategy is the spending function approach of Lan.\(^4\) Other statistical procedures such as stochastic limitation or conditional power approaches consider
negative stopping (i.e., stopping for lack of efficacy). These include stochastic limitation or conditional power procedures which allow for the early termination of a clinical trial if given the available trial information so far, the probability of reaching statistical significance in favor of the new treatment is small.\(^4\) There are also Bayesian or semi-Bayesian counterparts for each of these frequentist approaches. Some of these Bayesian and semi-Bayesian approaches are described in Roger and Berry\(^5\), Emerson\(^6\), and Grossman, Parmar, and Spiegelhalter\(^7\). Generally, stopping rules for interim analyses based on limited data (early termination) require more stringent p-values for stopping than later analyses, which can have stopping p-values somewhat near to nominal levels of significance. There seems to be an increase in the use of unscheduled interim analysis in confirmatory clinical trials, and the inappropriate and naive use of interim analysis practices in the name of operational/administrative interim analysis, interim analysis for safety, and/or sample size adjustment. The use of these practices for which there are no documented statistical strategies creates serious problems during the review process. Therefore, there is a need for formal statements and guidelines on their usefulness or lack thereof, at least for confirmatory clinical trials.

**5.2 Planned and Unplanned Interim Analysis**

Planned or unplanned operational interim analyses in confirmatory clinical trials that involve formal statistical methods that compare the relative treatment group differences and the dissemination of analysis results (either dictated by forces outside the clinical trial operations or not) should be treated as interim analyses. The need to adjust the nominal p-values after the conduct of such interim analyses is not mollified by the fact that such interim analyses were made on the basis of information external to the clinical trial operations. For retrospective operational interim analyses, there should be documentation of the rationale for such analyses, the retrospective analysis methods used for the assessment and proper protection of the overall Type I rate, and steps taken for the minimization of bias and protection of the data integrity. If it is believed that such operational analyses could not in principle lead to early termination of the clinical trial, assurance that no consequent early stopping or major changes in the design or patient recruitment could have occurred is necessary. Failure to do this casts doubt on the entire conduct of the clinical trial and delays the review and approval process of the drug.

These are perhaps the most difficult to handle and yet, the most common interim analysis issues statistical reviewers are faced with during the review process. For while there
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exist a number of formal statistical procedures for the adjustment of p-values for prospectively planned interim analyses (ie, interim analyses that are planned as part of the protocol), the statistical literature is very scanty in standard retrospective statistical procedures for the adjustment of p-values (for unplanned interim analyses). To the knowledge of this author, the only known works in this area are those of Geller and Pocock 8, Pocock and Hughes 9, and to some extent, that of Emerson6. According to these authors8,9, one approach is to assume that the accumulating data are continuously being looked at but interim analyses are carried out only when they (the data) look interesting. This is equivalent to a continuous sequential design, and the repeated significance testing sequential designs of Armitage, McPherson, and Rowe10 may be appropriate. This ad-hoc approach has been adopted by a number of statistical reviewers faced with problems of unplanned interim analyses during the review process of clinical trials. Besides this ad-hoc approach, the more flexible alpha spending function approach has also been suggested as a candidate for retrospective adjustment of p-values due to unplanned interim analyses when the exact number of unplanned interim analyses actually carried out is known. In this approach, pre-specification of the number of interim analyses to be carried out is not required since the overall Type I error rate is simply distributed (or spent) over the number of interim analyses actually carried out. Unplanned interim analysis is a serious issue that has not received much needed attention from the statistical community. Better statistical guidelines and more research are needed in this area.

Given the lack of standard statistical methods for retrospective adjustment of p-values due to unplanned interim analyses, unplanned interim analyses should be avoided as they can flaw the results of a well-planned clinical trial. Where such (unplanned) interim analyses are unavoidable, procedures should be in place to address this possibility and, when actually carried out, the study report must carefully explain why such analyses were necessary, the degree to which blindness had to be broken, and what subsequent actions were possible in principle. The performance of a clinical trial is only justified if the clinical investigators in advance consider ethical aspects and if an external ethical committee has approved the conduct of the study according to a defined protocol. Ethical aspects include the obligation that only the minimum number of patients should be entered onto the trial, which is necessary to achieve the study’s primary objective given previous experience with the specific treatment.
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5.3 Operational level requirement while conducting the clinical trial

Clinical trials need to be carefully monitored, so that decisions to stop early, whether based on trial data or external evidence, can be properly made and documented. What, in practical terms can be done? First, make a realistic assessment of possible scenarios, using general experience from clinical trials. Rigorous assessment of directly relevant trials should be carried out, using techniques such as metaanalysis. Subjective beliefs about the likely relative efficacy of the treatments, and the clinical benefits that would be required before a new treatment would be used routinely can also be documented at this stage, although these can be surprisingly variable, as illustrated by some work on a trial of treatment.

Mechanisms for stopping the trial must be identified, with lines of communication and responsibilities well-defined. The criteria for stopping a trial should be explicit. Mortality and excess toxicity are obvious endpoints to monitor, but more complex features such as quality of life are much more difficult to assess and analyse. A particular dilemma arises when considering which endpoints to monitor because only short-term results, such as tumour response, acute morbidity and early deaths, are available quickly, whereas the real value of many trials is their potential to give information on long term survival and late morbidity. By definition, decisions to stop have to be made primarily on the early information, and it is of importance to assess to what extent this can act as surrogate information for the longer term outcomes. Monitoring for toxicity is always worthwhile, but monitoring for efficacy is likely to be most beneficial when mature data are accruing fast relative to the entry of new patients.

If a trial does stop early, what are the priorities? The surviving trial patients should be informed of the position, which will be much easier if they gave genuinely informed consent. The next priority should be the release of full results, quickly, via peer-reviewed journals, although this is difficult given the current constraints of most journals.

The major fear is the possibility of undue harm (or lack of benefits) to trial patients. If the trial is not blind, as has to be the case with many cancer trials, suspicions of a difference may arise among participating clinicians, and unplanned interim analysis may lead to a dilemma. In a trial of second-line hormone therapy versus single agent chemotherapy it became evident that there was no early advantage to the group randomized to chemotherapy, although it is not clear whether this was based on clinical observation or ad hoc analysis. The authors say 'Having sought statistical advice, the trial was abandoned once sufficient events
had occurred to allow for sufficient statistical power in its analysis'. It is far better to plan in advance.

From the statistical viewpoint, monitoring methods can be classified according to whether the method is frequentist or Bayesian\(^\text{15}\) and comprehensive reviews of statistical aspects of monitoring can be found in Whitehead\(^\text{16}\), Jennison and Turnbull\(^\text{17}\) and Piantadosi.\(^\text{18}\) However, regardless of the specific method used, a key issue is that statistical rules are only a part of the question, as they tend to oversimplify the information relevant to the decision that must be taken. The decision to stop a trial before the prespecified final analysis should not be guided only by statistical considerations, but also by practical issues (toxicity, ease of administration, costs, etc.), as well as clinical considerations. For this reason it is preferable to refer to statistical methods as guidelines, rather than rules.\(^\text{19}\)

The decision to conduct an interim analysis should be based, first and foremost, on sound scientific reasoning that is guided by clinical and statistical integrity, standard operating practices for interim analyses, and regulatory concerns. Such a decision must not and should not be based on natural tendencies toward operational or academic curiosity. Currently, there are no standard statistical strategies for the adjustment of p-values due to unplanned interim analyses. Therefore, unplanned interim analyses should be avoided as they can flaw the results of a well planned clinical trial. More statistical research and guidance are needed in this area. In summary, good performance metrics enable greater understanding of study progress, far tighter control, more effective allocation of resources such as monitoring time, faster enrollment, and, in the larger scheme of things, shorter timelines and lower costs in operations and decision making process.

### 5.4 References


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5.5 Investigational Study Detail

Advanced NSCLC remains one of the most challenging and aggressive forms of lung cancer to be treated. The cytotoxic drug combinations have been found to give some advantage in survival but the severe side effects and poor quality of life remain a major concern for this approach. In last two decades or so, several immunomodulators together with cytotoxic drugs have been put under patients trials expecting a higher Th-1 type of response. These trials included treatment with BCG, Krestine, levamisol and heat killed Mycobacterium vaccae. None of these were found to be very helpful in reducing toxicity of therapy of cytotoxic therapy or in improving QoL of patients. Although Mycobacterium vaccae showed some promise in improving one year survival in a small study (n=28), its further exploration and potential have not been reported. In addition, in these trials, a potential negative interaction such as dose-dependent immunosuppression (myelosuppression) is a major concern in approaches like this.

In a preliminary Phase-IIa study of Test Drug in the management of advanced NSCLC, this immunomodulator was evaluated as an adjuvant therapy in a controlled clinical trial. The standard therapy employed was combination chemotherapy in form of cisplatin and etoposide along with radiotherapy. The group receiving Test Drug tolerated the chemotherapy and radiotherapy well and completed it as planned in contrast to premature stoppage of radiotherapy in 50% of patients in control group. Improvement in quality of life as measured by Karnofsky performance status was significantly better in patients receiving Test Drug. Similarly effect on lung cancer was also significant with two-third showing regression in tumor size in Test Drug group compared to control. This also got reflected in improvement in lung function with improved response rate which was durable in nature. Addition of Test Drug also resulted in significant reduction in hematological and gastrointestinal side effects of chemotherapy/radiotherapy.

5.6 Interim Analyses, Data Monitoring and Decision Making

This interim analysis under study was commissioned by DSMB for the cancer trials. Before this interim analysis was performed, all patients related CRF were retrieved in order to have up to date data of first 82 (1/3rd) patients from screening visit to visit 5th as per study calendar. TMF was updated on with all latest safety reports including all deaths during the conduct of the trial till date. However, the data included in this interim analysis consists of only those patients who completed four cycles of chemotherapy treatment with 1 month of follow up period. (till 5th visit). In other words this interim analysis has been performed.
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based on intend to treat (ITT) irrespective of the patient have completed their duration of treatment as per protocol or not. These patients were recruited & followed up for the period of 1 month.

5.6.1 Objectives and Endpoints for Interim Analysis:

Not all objectives and endpoints described in the study protocol have been considered for this interim analysis. As decided in DSMB meeting following objective and endpoints were analyzed in current interim analysis.

Efficacy:

A. Analysis and comparison of Time to tumor progression in both the arms.
B. Intent to Treat Analysis for Overall Survival in both the arms.
C. Per Protocol Analysis for Overall Survival in both the arms at 2nd & 4th Chemotherapy cycle.
D. Intent to Treat for Progression Free Survival in both the arms.
E. Per Protocol Analysis for Progression Free Survival in both the arms at 2nd & 4th Chemotherapy cycle.
F. Overall Tumor Response.
G. Analysis and comparison of Quality Of Life (QoL) as per FACT - L in both the arms.

Safety:

Comparison of hematological & systemic toxicities and all other serious adverse events (reported either as adverse or serious adverse event) in both the arms were made with respect to the frequency, severity and causality.

5.6.2 Baseline Data:

Out of total sample size of 246 patients, 82 patients were eligible for interim analysis. 76 patients are included for QoL analysis and 71 patients for Tumor response evaluation. 5 patients were excluded from QoL assessment (1 in control, 4 in test arm) because of consent withdrawal even before first follow up QoL visit.

5.6.3 Planned and Analyzed

Interim analysis has been done after 82/246 (1/3rd) of the enrolled patients complete four months of their study duration i.e. 4 Chemotherapy cycles and 1 month follow up.
5.7 Decisional Stopping Rules

Decisions on early stopping or not need to be based on wise judgments interpreting the totality of available evidence, both in the current study considering primary and other efficacy outcomes and safety issues and in other external evidence especially from related trials. If a trial is for regulatory approval, the sponsor and trialists should be encouraged not to stop early unless there is overwhelming evidence of treatment superiority, since the regulators require substantial evidence of both efficacy and safety, often in at least 2 trials reaching their intended full size and patient follow-up.

In this study we have decided the stopping rule as per the recommendations of DSMB:-

- If progression free survival is not significant at given $\alpha$.
- If there is no shrinkage in tumor size & absence of tumor lesions at given $\alpha$.
- If there is no improvement in quality of life of patients at given $\alpha$.
- If there is severe adverse events - hematological & non- hematological at given $\alpha$.
- If there is unexpected death patterns are observed during the trial.

(*Given $\alpha$ equal to $<< 0.05$ appropriate for $\alpha$ spending at the interim analysis).
5.8 Results

Following are the brief finding and facts of the investigational study-

**TTP function for Test & Control drug**

![TTP Analysis](image)

**Figure 5.1:** Shows that median survival time in the Test arm is 152 days and in the Control arm 118 days, \((p=0.2773)\).

*However, patients treated with test drug* take more time for disease to progress than those treated with control drug. In test arm expected events (disease progression) are 16 whereas observed was only 11. In control arm expected events are 11 whereas observed are 12.
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Intent to Treat Analysis for Overall Survival

![Graph showing survival distribution for Intent-to-Treat analysis.](image)

**Figure 5.2:** Total 246 patients were analyzed; the median overall survival in the ITT population was 206 and 194 days in the test and control arms, respectively. [hazard ratio 0.86 (95% CI: 0.62-1.16), p=0.37]

Per Protocol Analysis for Overall Survival

![Graph showing survival distribution for per protocol analysis.](image)

**Figure 5.3:** In the 2nd chemotherapy cycle a total 195(T-90, C-105) patients were analyzed. The median overall survival for the Test arm was 251 days and for control arm 209 days. [hazard ratio 0.69 (95% CI: 0.52-1.03), p=0.06]
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Figure 5.4: At the end of 4th Chemotherapy cycle the total 151 (T-72, C-79) patients were analyzed where Median overall survival of Test arm was 297 days and Control arm 231 days [hazard ratio 0.63 (95% CI: 0.41-.97), p=0.03]

Intent to Treat for Progression Free Survival

Figure 5.5: The analysis of intent to treat for PFS considering total 246 patients shows the median progression free survival for the Test arm was 201 days and for Control arm 96 days [hazard ratio 0.67 (95% CI: 0.46-0.99), p=0.049]
Per Protocol Analysis for Progression Free Survival

**Figure 5.6: 2\textsuperscript{nd} Chemotherapy cycle**

In Per protocol analysis for PFS at 2\textsuperscript{nd} chemotherapy cycle total 195 (T-90, C-105) patients were evaluated. The median overall survival of Test arm patients was 225 days and another arm that is Control arm was 103 days. [hazard ratio 0.47 (95% CI: 0.31-0.74), p=0.002]

**Figure 5.7: 4\textsuperscript{th} Chemotherapy cycle**

While at the 4\textsuperscript{th} Chemotherapy cycle of total 151 (T-72, C-79) patients, the median overall survival was 257 days for Test arm and 159 days for control arm. [hazard ratio 0.41 (95% CI: 0.27-0.71), p=0.001]
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Overall Tumor Response

Table 5.1

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<td>Final Analysis</td>
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Analysis and comparison was done for the Interim and Final Analysis, though there was no statistically significant difference observed, the test arm response trend was better than control arm when disease control rate and response rate analysis was performed.

In the Test arm patients there were 14 responders out of 37 patients at the time of interim analysis but the number increased to 57 out of 136 patients during the final analysis while in the control arm only 11 responders were observed in the interim analysis and 43 responders at the time of final analysis out of 34 and 71 patients respectively.
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Quality of Life

Interim Analysis

- No statistically significant difference between test and control arm with p-value=0.2601 and p-value=0.3462 for TOI and Total Score respectively.

Final Analysis

No significant differences between the test arm and control arm was observed all the parameters were evaluated like-

- Physical Well Being (PWB; p=0.7478),
- Emotional Well Being (EWB; p=0.9424),
- Functional Well Being (FWB; p=0.1961),
- Additional Concern (AC; p=0.8549) and
- Social Well Being (SWB; p=0.2057).

There were no significant differences between test and control arms when TOI (p=0.5887) and TS (p=0.4783) of final visit was compared between them.

Serious Adverse Effects

- Deaths before completion of Tx = 57 (T- 22, C- 35, none of the death case was observed due to study drug).
- Per protocol deaths: 103 (T- 44, C- 59, No significance difference , p=0.1134).
- Hospitalizations associated with serious adverse events - statistically non-significant, analyzed based on causality (p=0.1674), AE outcome (p=0.1043) and particularly system related AEs (p=0.2435).
- Medically significant adverse events - statistically non-significant, analyzed based on causality (p=0.5760), AE outcome (p=0.9061) and particularly system related AEs (p=0.6136).
- Both arms had fewer and comparable grade 3 (T-11, C-12) and grade 4 (T-1, C-0) toxicities.
- Total alive patients at cut-off date: 67(T- 35, C- 32) and
- At last contact: 31(T- 19, C-12)
5.9 Discussion and Overall Conclusions

In the present well designed Phase-II trial, we further examined the hypothesis closely that the heat killed Test Drug vaccine used as an adjuvant together with cisplatin and paclitaxel would be non-inferior or better than the standard combination chemotherapy of cisplatin and paclitaxel. The expectation was based on previous experiments as cited above as well as the fact that Test Drug is a very potent innate (Th-1) response enhancer and can not only overcome the immunosuppression commonly seen in NSCLC treated with cytotoxic agent, but actually can contribute to a significant delay in diseases progression and improvement in quality of life. The optimal duration therapy (number of cycles) for the cisplatin and paclitaxel combination was set at 4 cycles in both arms in this study. This was because in previous studies where 3-6 cycles were examined for optimization of chemotherapy duration for survival, it was found that there was hardly any added benefit of using more than 4 cycles of combination chemotherapy. In fact, it was suggested that fatigue, nausea and vomiting were more frequent in those patients who received more than 4 cycles than those who received up to 4 cycles. Interventions in both arms were well tolerated in both arms. However, the side effect of injection site reaction was more in the test arm employing Test Drug as an adjuvant as expected. Adverse event data and serious toxicity data (SAE) were similar and comparable for both the sites. Hematological and non-hematological toxicities were comparable among both the arms.

The median overall survival (OS) in paclitaxel and cisplatin treated patients completing 4th chemotherapy cycle was little less than 8 months where as on addition of Test Drug as an adjuvant to this regimen, it was increased by slightly more than 2 months. The progress free survival perhaps endorses the adjuvant efficacy of Test Drug more than so does the overall survival. In all analyses carried out up to and beyond visit IV, which marked the completion of as many chemotherapy cycles in both arms, progress free survival times were consistently and significantly better in the test arm than that of the control arm. The median PFS in the paclitaxel and cisplatin group was a little more than 5 months, which is very common among Indian advanced NSCLC patients. This study demonstrates that if Test Drug is used as an adjuvant with the same chemotherapy, a progress free survival gain of approximately three months can be achieved on an average. To the best our knowledge this is the largest efficacy margin that any trial has reported so far under comparable conditions. Another highlight of the collected data from this trial is that the intent to treat analysis of PFS is entirely consistent in medical and statistical significance with the protocol compliant (PP)
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data. The implication is that in the phase III or future clinical practice set up, we may expect very similar results. Based on previous study with Test Drug in NSCLC, it was postulated that Test Drug might improve quality of life in NSCLC patients. The results of present study showed with the addition of Test Drug in cisplatin and paclitaxel regimen did not show significant improvements in QOL and the data in both the arms were similar.

Though tumor response was not significantly higher in the test arm as compared to control arm, 4 patients showed complete responses in test arm which was not in the case of control arm. Although the numbers of partial response and stable responses were comparable in the control arm and test arm for patients completing 4B visit, an average of 5.41% gains in disease control rate (88.97% in test arm versus 83.23 % in control arm) and 10.67% (46.34% in test arm versus 37.61% in control arm) mark the improved response rate comparisons on addition of Test Drug to the cisplatin and paclitaxel regimen. Test Drug being primarily a potent but nonspecific immunostimulant, the relative response rate was highly encouraging in this trial. The context of an immunomodulator enhancing tumor response, and subsequently the progress free survival time need not stop only delay of the disease exacerbation and improvement in quality of life, an impression of this efficacy gain can extent up to an increased overall survival time. In fact, in the present study, the OS data of the protocol compliant patients reflect the same positive trend for the test arm as discussed above for the PFS data. In PP analysis, there was a significant gain of more than 2 months survival time in the Test Drug arm. The ITT reflected a similar medically advantageous trend without reaching statistical significance.

Both the baseline and extraneous hazards (higher stage of disease, intervention) were reduced by the adjuvant efficacy of Test Drug. In the protocol compliant patients, a relative risk reduction of more than 51% was computed in disease progress free data. Even in overall survival data this reduction in relative risk was about 34%. This implies that Test Drug may be working at a level more than its non-specific immunomodulation towards more Th-1 response. While the detailed mechanism of this additional anti-cancer activity needs to be studied with appropriately designed studies in future, the prospect of present data for future phase III studies or a fast track regulatory review is very high.

The present data can also be adapted in a design for a larger study which would unequivocally establish efficacy and safety of Test Drug as an adjuvant with platinum-taxane standard combinations.
5.10 Rational Conclusions

- DSMB recommended to continue the study after interim analysis.
- Based on present data of IA and Final analysis consistency were observed in overall tumor response, QoL, SAEs and death patterns.
- Per protocol analysis of overall survival and progression free survival clearly indicates that Test arm are performing better.
- Though overall tumor response & quality of life is not significantly different but test arm response trend was better than control arm in disease control rate.
- SAEs/Death pattern was acceptable considering disease stages (no death is reported due to test drugs).
- Results can be adapted in a design for larger study which would establish efficacy and safety of test drug Test Drug as an adjuvant with platinum-taxane standard combinations.