Official Title of the study	**LUNAR: Pivotal, randomized, open-label study of Tumor Treating Fields (TTFields) concurrent with standard of care therapies for treatment of stage 4 non-small cell lung cancer (NSCLC) following platinum failure**
NCT number	**NCT02973789**
Document Date	**April 5, 2023**

Statistical Analysis Plan

Clinical investigation title	LUNAR: Pivotal, randomized, open-label study of Tumor Treating Fields (TTFields) concurrent with standard of care therapies for treatment of stage 4 non-small cell lung cancer (NSCLC) following platinum failure
Clinical investigation identification	EF-24
Investigational device	NovoTTF-200T (150kHz output frequency)
Document number	[redacted]
Version	[redacted]
Document Date	[redacted]
Sponsor	Novocure GmbH
CRO name and internal study ID	[redacted] Study ID: [redacted]

Revision History

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Reviewers

The following reviews of the SAP were conducted:

Name and Title	Role	Version Last Reviewed	Company/ Organization
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Glossary of Abbreviations

Abbreviation	Term
AE	Adverse Event
ADE	Adverse Device Effect
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BSC	Best Supportive Care
BUN	Blood Urea Nitrogen
CA	Competent Authority
CI	Confidence Interval
Cm	Centimeter
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DD	Device Deficiency
DMC	Data and Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
irRECIST	Immune-Related Response Evaluation Criteria In Solid Tumors
ITT	Intent to Treat
MRI	Magnetic Resonance Imaging
MST:	Mean Survival Time
NSCLC	Non-Small-Cell Lung Cancer
OS	Overall Survival
PD-L1	Programmed Death Ligand 1
PFS	Progression Free Survival
PT	Prothrombin time
PTT	Partial Thromboplastin Time
QLQ C-30	EORTC's Quality of life Questionnaire
QLQ- LC13	EORTC's Cancer Quality of life Questionnaire Lung Cancer Module
RECIST:	Response Evaluation Criteria In Solid Tumors
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAF	Safety Population
SOC	Standard of Care
TTFields	Tumor Treatment Fields
UADE	Unanticipated adverse device effect
ULN	Upper Limit Normal
USADE	Unanticipated Serious Adverse Device Effect

1. SOURCE DOCUMENTS

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	[redacted]	[redacted]
eCRF	[redacted]	

2. PROTOCOL DETAILS

2.1. Study Objectives

2.1.1. Primary Objectives

To determine if stage 4 NSCLC patients treated with TTFields concomitant with docetaxel or immune checkpoint inhibitors following progression while on or after platinum treatment have a superior overall survival compared to patients who are treated with docetaxel or immune checkpoint inhibitors without TTFields.

2.1.2. Secondary Objectives

1. To determine if the overall survival of patients treated with docetaxel + TTFields following progression while on or after platinum treatment is superior to the overall survival of patients treated with docetaxel alone.
2. To determine if the overall survival of patients treated with immune checkpoint inhibitors + TTFields following progression while on or after platinum treatment is superior to the overall survival of patients treated with immune checkpoint inhibitors alone.
3. To determine if the overall survival of patients treated with docetaxel + TTFields following progression while on or after platinum treatment is non-inferior to the overall survival of patients treated with immune checkpoint inhibitors alone.
4. To determine if the progression-free survival of patients treated with docetaxel or immune checkpoint inhibitors + TTFields following progression while on or after platinum treatment is superior to the progression-free survival of patients treated with docetaxel or immune checkpoint inhibitors alone, based on the RECIST criteria.
5. To compare the overall radiological response rate (ORR, based on RECIST criteria) of patients treated with docetaxel or immune checkpoint inhibitors +

TTFields following progression while on or after platinum treatment compared with that of patients treated with docetaxel or immune checkpoint inhibitors alone.

6. To compare the quality of life of patients treated with docetaxel or immune checkpoint inhibitors concomitant with TTFields following progression while on or after platinum treatment to that of patients who are treated with docetaxel or immune checkpoint inhibitors without TTFields, using the EORTC QLQ C30 questionnaire with LC13 addendum.
7. To analyze the effects of NovoTTF-200T with each type of immune checkpoint inhibitor on OS and PFS.
8. To analyze the effects of NovoTTF-200T on OS and PFS within each histological subgroup (squamous and non-squamous).
9. To analyze whether average monthly usage of over 75% of the time leads to better OS and PFS outcomes, as seen in glioblastoma patients treated with TTFields.
10. To assess adverse events, severity and frequency, associated with treating patients with docetaxel or immune checkpoint inhibitors concomitant with TTFields using the NovoTTF-200T System.

2.2. Overall Study Design

This is a pivotal prospective, randomized, open-label multicenter study. This randomized study is designed to test the efficacy and safety of TTFields, using the NovoTTF-200T System, concurrent with standard therapies for stage 4 non-small cell lung cancer (NSCLC) patients, following progression while on or after platinum based treatment. The study population are the patients with histology based diagnosis of stage 4 NSCLC, above 22 years of age, following disease progression on or after receiving platinum based chemotherapy. Patients will be stratified as below:

- Arm I: Patients who receive docetaxel or immune checkpoint inhibitor concomitant with TTFields using the NovoTTF-200T System set to an output frequency of 150kHz.
- Arm II: Patients who receive docetaxel or immune checkpoint inhibitors without TTFields.

On both arms, patients receiving docetaxel whose lung cancer progresses based on RECIST criteria, or receiving immune checkpoint inhibitors whose lung cancer progresses based on irRECIST criteria, will switch to a next line of treatment according to local practice.

[redacted]

[redacted]

Patients on both arms should also receive the best supportive care available at each site. Following progression patients may be offered standard NSCLC-directed therapy and salvage therapy based on local practice at each site. Surgery and radiation therapy are allowed prior to disease progression.

The overall schedule of the study is as follows:

2.3. Sample Size and Power

[redacted]

3. EFFICACY AND SAFETY VARIABLES

3.1. Primary Efficacy Endpoint

Overall survival (OS) of patients treated with TTFields concomitant with docetaxel or immune checkpoint inhibitors compared to patients treated with docetaxel or immune checkpoint inhibitors alone (superiority). Overall survival will be measured as time from randomization to date-of-death of any cause or censored at the last follow up date. OS (months) will be calculated as:

[redacted]

3.2. Secondary Efficacy Endpoints

3.2.1. Key Secondary Efficacy Endpoints

[redacted]Overall survival of patients treated with docetaxel + TTFields compared to overall survival of patients treated with docetaxel alone (superiority). [redacted]

2. Overall survival of patients treated with immune checkpoint inhibitors + TTFields compared to overall survival of patients treated with immune checkpoint inhibitors alone (superiority). [redacted]

3.2.2. Additional Secondary Efficacy Endpoints

1. Overall survival of patients treated with docetaxel + TTFields compared to overall survival of patients treated with immune checkpoint inhibitors alone (non-inferiority). [redacted]

2. Progression-free survival of patients treated with docetaxel or immune checkpoint inhibitors + TTFields compared to progression-free survival of patients treated with docetaxel or immune checkpoint inhibitors alone, based on RECIST.

   Progression-free survival is defined as the time from the date of randomization until the date of disease progression according to RECIST or death [redacted]

3. Overall radiological response rate of patients treated with docetaxel or immune checkpoint inhibitors + TTFields compared with that of patients treated with docetaxel or immune checkpoint inhibitors alone.

   Radiological response is defined as patients with best overall response (BOR) of partial response (PR) or complete response (CR) based on RECIST criteria.

   Overall radiological response rate (ORR) is defined as proportion of randomized patients with radiological response (CR or PR) following study treatments.

4. Quality of life of patients treated with docetaxel or immune checkpoint inhibitors concomitant with TTFields compared to that of patients who are treated with docetaxel or immune checkpoint inhibitors without TTFields, using the EORTC QLQ C30 questionnaire with LC13 addendum.

[redacted]

5. Analyses of the effects of NovoTTF-200T with each type of immune checkpoint inhibitor [redacted] on OS and PFS will be performed.

6. Analysis of the effects of NovoTTF-200T on OS and PFS will be tested within each histological subgroup (squamous and non-squamous).

7. The effect of treatment usage with NovoTTF-200T (as calculated from the device log file) will be tested to determine whether average monthly usage of over 75% of the time leads to better OS and PFS outcomes, as seen in glioblastoma patients treated with TTFields.

[redacted]

3.3. Safety Variables

3.3.1. Extent of Exposure [redacted]

[redacted]

Extent of exposure to NovoTTF-200T will be summarized descriptively for the patients who randomized to the NovoTTF-200T arm as:

[redacted]

3.3.1.2. Exposure to Standard of Care

Standard of care in this study contains [redacted] drugs: [redacted] For each drug, the following variables will be determined:

[redacted]

3.3.2. Adverse Events (AEs)

All adverse events (AEs) recorded on the eCRF will be coded using the MedDRA dictionary [Version 23.0]. The adverse event reporting period will begin immediately following randomization. Adverse events will be collected until last study follow up visit and for [redacted] following treatment termination

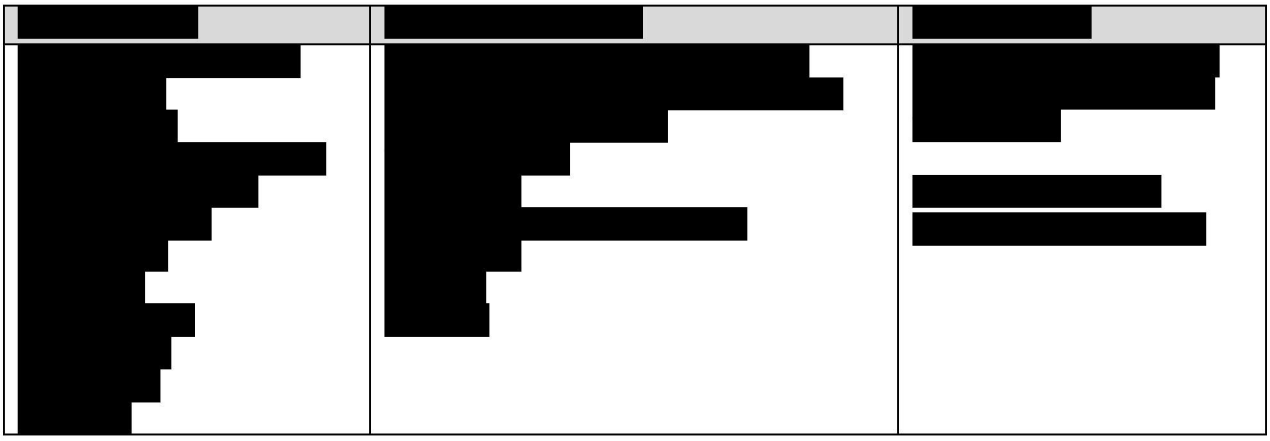
Treatment-emergence adverse events (TEAEs) are events with start date on or after the first date of any study treatment (including SOC or TTFields), or events with start date prior to the date of first treatment whose severity worsens on or after the date first treatment.

Assessment of AE severity will be based on the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 5.0.

The relationship between an AE and study device is assessed as definite, probable, possible, unlikely, or none. A device-related AE is an AE considered by the investigator as definitely, possibly, or probably related to study device. [redacted]

3.3.3. Laboratory Evaluations

[redacted]



3.3.4. Vital Signs

[redacted]

[redacted]

3.3.5. Physical Examination

Physical examination assessments including [redacted] will be performed according to the study schedule [redacted]

4. PHARMACOKINETIC/PHARMACODYNAMIC VARIABLES

Not applicable.

5. ANALYSIS POPULATIONS

5.1. Efficacy Population

The efficacy analysis populations will consist of all randomized patients treated with TTFields + docetaxel or immune checkpoint inhibitors verses patients treated with treatment of docetaxel or immune checkpoint inhibitors alone.

5.2. Safety Population

The safety analysis (SAF) dataset will include all patients who received any amount of TTFields or standard of care in the study. Safety subjects are analyzed according to the actual treatment received.

6. DATA HANDLING

6.1. Time points and Visit Windows

[redacted]

[redacted]

- [redacted]

6.2. Handling of Dropouts, Missing Data, and Outliers

[redacted]

7. STATISTICAL METHODS

7.1. General Principles

All data processing, summarization and analyses will be performed using [redacted] of the SAS® statistical software package.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 1 Statistical Analysis General Principles

Principle	Value
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Principle	Value
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

7.2. Subject Disposition and Data Sets Analyzed

Subject disposition will include all subjects and will be listed and summarized by treatment group and overall and will include [redacted]

[redacted]

[redacted]

7.3. Protocol Deviations

All protocol deviations will be listed. [redacted].

7.4. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment group and overall for ITT populations.

Standard descriptive statistics will be presented for the continuous variable of:

[redacted]

The total counts and percentages of subjects will be presented for the categorical variables of:

- Gender (Female, Male)
- [redacted]

- Childbearing potential (Yes, No), if female
- If no, reason (Surgically sterile, Post-menopausal, Other)

- Race [redacted]
- Ethnicity [redacted]
- Cigarette smoking status [redacted]
- ECOG Performance status (0, 1, 2)
- Standard of care treatment from (Immune checkpoint inhibitor, Docetaxel)
- Tumor histology from CRF (Non-squamous, Squamous)
- Region [redacted])

[redacted]

- [redacted]
- Treatment received for NSCLC diagnosis (Yes, No)
- Received any procedures for NSCLC (Yes, No)

7.5. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 23.0]. All medical history will be listed, and the number and percentage of subjects with any medical history will be summarized for safety population by system organ class (SOC) and preferred term (PT) for each treatment group and overall. [redacted].

7.6. Previous and Concomitant Medications

A listing of prior NSCLC therapies and procedures will be presented.

Medications received prior to or concomitantly with treatment will be coded using WHODrug Dictionary enhanced [March 2016], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

[redacted]

7.7. Efficacy

7.7.1. Primary Efficacy Analysis

The primary endpoint is to compare overall survival (OS) of patients treated with TTFields concomitant with standard of care of docetaxel or immune checkpoint inhibitor (SOC) versus patients treated with SOC alone (superiority).

The primary endpoint will be summarized using Kaplan-Meier (KM) estimate. The treatment difference will be tested using a [redacted] in ITT population. [redacted]

The primary endpoint will be met if the null hypothesis is rejected.

[redacted]

[redacted]

[redacted]

[redacted]

7.7.2. Secondary Efficacy Analysis

The key secondary endpoints will be tested hierarchically only if the primary endpoint is met (hierarchical testing) in order to avoid multiplicity in type I error.

The study is powered to detect an alternative hypothesis of HR <1.

The primary objective is to determine if SOC+TTF is superior to SOC alone which is accomplished by rejecting H_0[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] The overall survival will be summarized using Kaplan-Meier (KM) estimate. The median, 25th and 75th percentiles of OS with 95% CIs will be estimated using the KM method for the two treatment groups. [redacted]

[redacted]

7.7.3. Exploratory Secondary Efficacy Analysis

7.7.3.1. Overall Survival in Docetaxel+TTFields vs Immune Checkpoint Inhibitor Alone

Analysis of OS will be performed to test whether TTFields with docetaxel is non-inferior to immune checkpoint inhibitors alone. The non-inferiority will be tested using [redacted] with the stratification factors of standard of care therapy and tumor histology. [redacted] Hazard ratio and the corresponding 95% CI will be presented. [redacted]

[redacted]

The median, 25th and 75th percentiles of OS with 95% CIs will be estimated using the KM method for the two treatment groups. [redacted]

7.7.3.2. Progression-free Survival (PFS)

The effect of TTF+SOC over SOC alone for PFS will be estimated using [redacted] test at an alpha level of 0.05. [redacted] stratification factor will be removed from the analysis.

The median, 25th and 75th percentiles of progression-free survival with 95% CIs will be estimated using the Kaplan-Meier method for the two treatment groups. [redacted]

7.7.3.3. Overall Radiological Response Rate

Overall radiological response rate (ORR) and its two-sided 95% confidence interval, which is based on the exact binomial distribution[redacted] will be presented.

The difference of ORR between the patients treated with TTFields concomitant with SOC and the patients treated with SOC alone, as well as the associated 2-sided 95% CI will be calculated using [redacted]

[redacted]

7.7.3.4. Quality of Life Questionnaire Scores

Scores from 0-100 will be derived for all multi-item or single item scales of the EORTC QLQ-C30 and QLQ-LC13.

For EORTC QLQ-C30, [redacted]

[redacted]

7.7.3.5. Effects of NovoTTF-200T with Each Type of Immune Checkpoint Inhibitors on OS and PFS

Analysis of the effects of NovoTTF-200T with each type of immune checkpoint inhibitors will be performed in these treatment groups:

- Nivolumab +TTFields vs Nivolumab alone
- Pembrolizumab +TTFields vs Pembrolizumab alone
- Atezolizumab +TTFields vs Atezolizumab alone

7.7.3.5.1. Overall Survival

The treatment difference in OS will be performed using [redacted]

The median, 25th and 75th percentiles of OS with 95% CIs will be estimated using the Kaplan-Meier method for each treatment group. [redacted]

[redacted]

7.7.3.5.2. Progression-free Survival

The treatment difference in PFS will be performed using [redacted]

The median, 25th and 75th percentiles of PFS with 95% CIs will be estimated using the Kaplan-Meier method for each treatment group. [redacted].

[redacted]

7.7.3.6. Effects of NovoTTF-200T on OS and PFS Within Each Histological Subgroup

Analysis of the effects of NovoTTF-200T on OS and PFS will be performed in each histological subgroup:

- Squamous: SOC + TTFields vs SOC alone
- Non-squamous: SOC + TTFields vs SOC alone

7.7.3.6.1. Overall Survival

The treatment difference in OS in each subgroup will be performed using [redacted]

The median, 25th and 75th percentiles of OS with 95% CIs will be estimated using the Kaplan-Meier method for each treatment group in each subgroup. [redacted]

[redacted]

7.7.3.6.2. Progression-free Survival

The treatment difference in PFS in each subgroup will be performed using [redacted]

The median, 25th and 75th percentiles of PFS with 95% CIs will be estimated using the Kaplan-Meier method for each treatment group in each subgroup. [redacted]

[redacted]

7.7.3.7. Effect of Treatment Compliance with NovoTTF-200T

To test whether average monthly compliance of NovoTTF-200T over 75% of the time leads to better OS and PFS outcomes, the analysis of the effect of treatment compliance with NovoTTF-200T will be performed in SOC + TTFields treatment group as:

Average monthly usage > 75% vs <= 75%

7.7.3.7.1. Overall Survival

The difference in OS between [redacted] groups will be performed using [redacted]

The median, 25th and 75th percentiles of OS with 95% CIs will be estimated using the Kaplan-Meier method for each compliance group. [redacted]

[redacted].

7.7.3.7.2. Progression-free Survival

The difference in PFS between [redacted] groups will be performed using [redacted]

The median, 25th and 75th percentiles of PFS with 95% CIs will be estimated using the Kaplan-Meier method for each compliance group. [redacted]

[redacted]

7.7.3.8. Salvage Therapy

The number and percentage of subjects who have reporting of taking salvage systemic therapy will be summarized by agent and treatment group.

All salvage treatment data will be listed.

7.7.4. Sensitivity Analysis

[redacted]

7.7.5. Subgroup Analysis

[redacted]

7.7.6. Poolability analysis

[redacted]

7.8. Safety

7.8.1. Extent of Exposure [redacted]

7.8.1.1. Exposure to NovoTTF – 200T

[redacted] usage will be summarized descriptively for the patients who randomized to the NovoTTF arm. The total

counts and percentages of subjects will be presented for the categorical variables of:

[redacted]

[redacted].

7.8.1.2. Exposure to Standard of Care

Standard of care in this study contains [redacted] drugs: [redacted] For each drug, number of cycles completed, total dose administered, and duration of exposure will be summarized by each treatment group in safety population using continuous descriptive statistics.

[redacted]

7.8.2. Adverse Events

An overview table will summarize the number and percentage of subjects with at least one of the following AEs by treatment group and overall:

[redacted]

A similar overall table summarizing treatment emergent AE will also be created.

The number and percentage of subjects reporting each AE will be summarized by System Organ Class and Preferred Term (PT) for the Safety population. Tables will be sorted alphabetically by System Organ Class. PTs will be sorted by descending overall total. The following summaries will be produced:

[redacted]

[redacted]

All AE data will be listed by treatment group. [redacted].

7.8.3. Laboratory Evaluations

All laboratory data will be reported in International System of Units (SI) units. [redacted]

Laboratory data will be summarized by treatment group, overall, and visit using standard descriptive statistics for the Safety population. Changes from baseline will also be summarized.

For [redacted], shift tables presenting from baseline to worst post baseline result will be provided for each treatment group.

For each laboratory analyte, [redacted].

7.8.4. Vital Signs

Vital signs data and changes from baseline in vital signs will be summarized by treatment group, overall, and visit using standard descriptive statistics for the Safety population.

7.8.5. Physical Examination

Physical examination data will be listed. [redacted]

7.9. Interim Analysis

Two interim analysis will be performed on the OS data available [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8. CHANGES IN PLANNED ANALYSIS

[redacted]

[redacted]

[redacted]

[redacted] of [redacted]

9. REFERENCES

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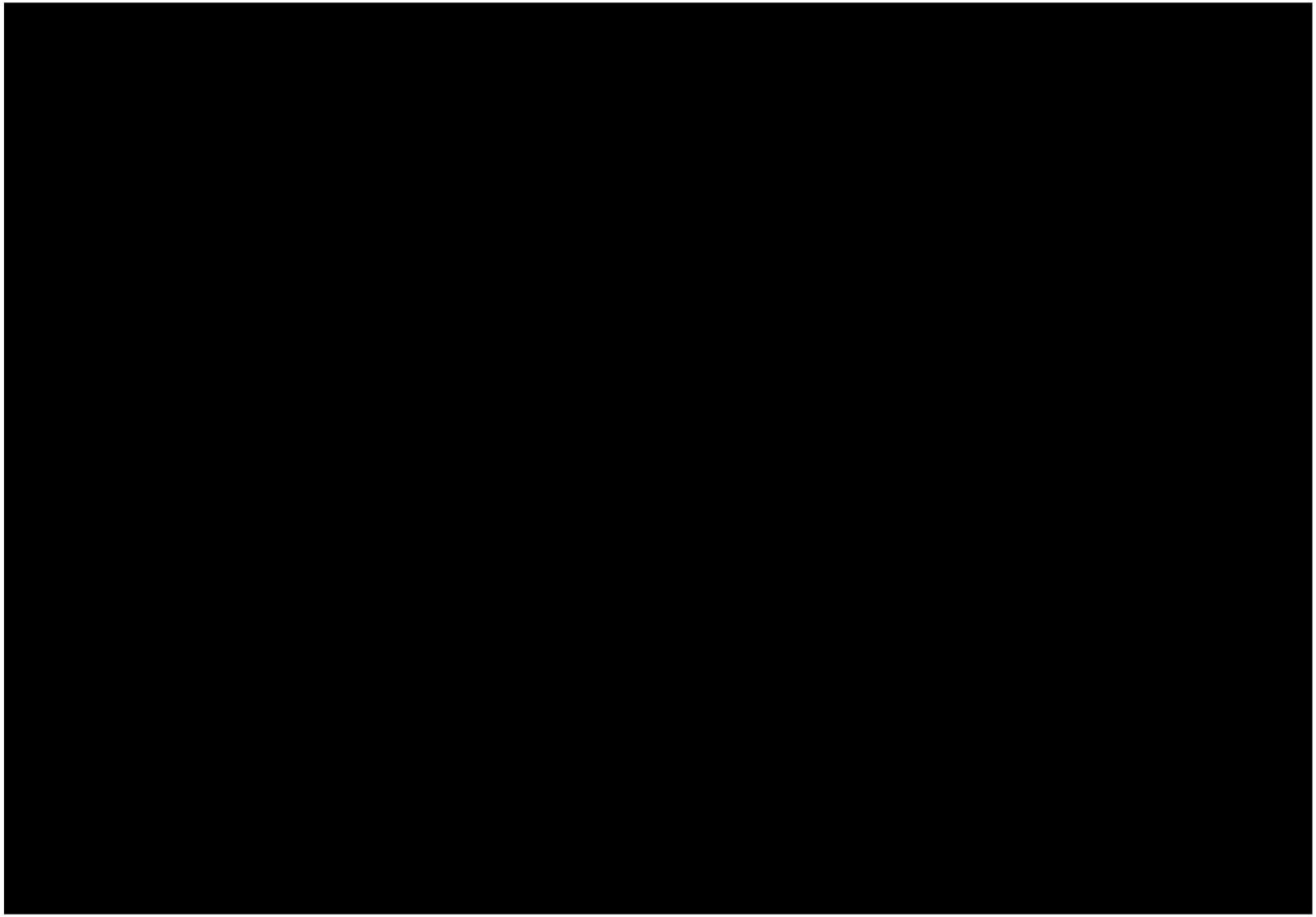
10. APPENDICES

10.1. EF-24 Study Calendar



10.2. Scoring algorithm for the EORTC-QLQC30

[redacted]

[redacted]

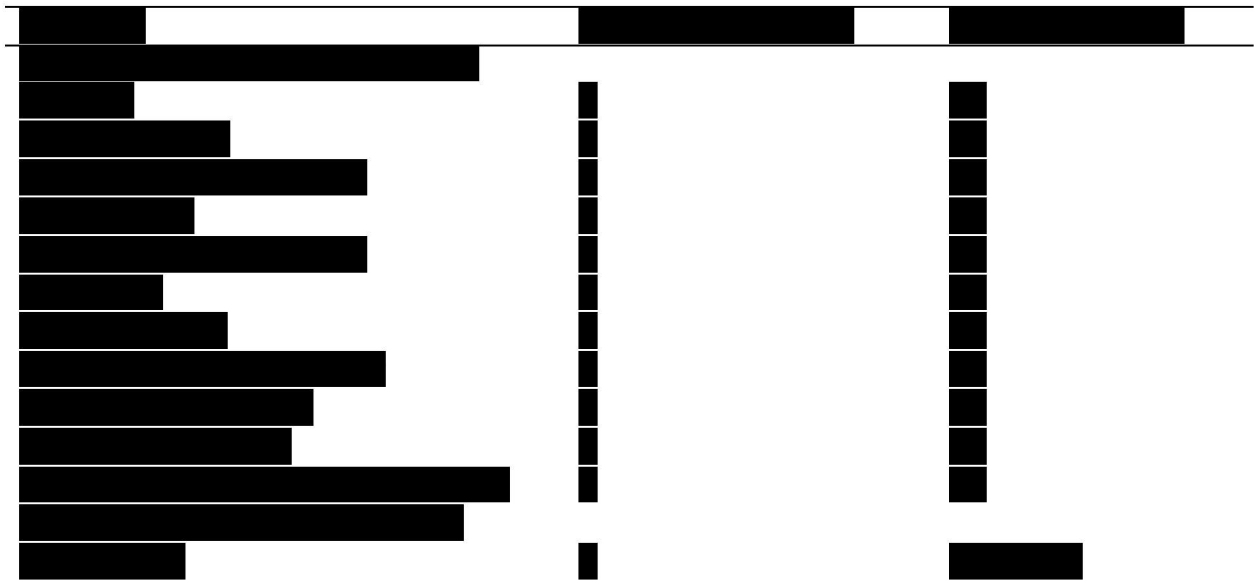
[redacted]

[redacted]

10.3. Scoring algorithm for the LC13

[redacted]

[redacted]



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Signature Page

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Approvers:

Date:

[redacted]

Date:

[redacted]