1. Post database lock Part 1: Primary study outcome (Progression-free and Overall) Survival Analysis Report

1. Introduction

This updated report summarises the time-to-event (survival) analyses performed for the trial's **primary study endpoints**, comparing treatment versus control for Progression-Free Survival (PFS) and Overall Survival (OS). Analyses were conducted in accordance with the Statistical Analysis Plan (SAP). They included univariate and multivariable Cox proportional hazards models, with adjustments for key prognostic factors and consideration of center effects.

Analyses of **secondary endpoints** are currently being conducted by the study biostatistician. The secondary endpoint results are expected to be finalised and available by the end of January 2026.

2. Methods

2.1. Data Preparation

To ensure consistency, death and progression dates were systematically merged across datasets. Death dates were recorded in multiple sources, including EOS, SAE, and 5-year follow-up CRFs. When only one death date was available, it was retained. If multiple sources provided the same date, it was used without modification. In cases where conflicting dates were found, the earliest date was selected unless further clarification was needed. Similarly, progression dates were recorded under different columns, requiring comparison across datasets. The earliest available progression date was selected for each patient to maintain consistency in the analysis.

Event Derivation

Progression-Free Survival (PFS)

For each patient, we determined whether a PFS event occurred and assigned the appropriate event date:

- **If a progression date or death date was present:**
  - The patient was classified as having a PFS event (**PFS_event = 1**).
  - The earliest of the two dates was used as the PFS event date (**PFS_DATE**).
- **If neither progression nor death occurred:**
  - The patient was considered censored (**PFS_event = 0**).
  - The censoring date was defined as the earliest available date among:
    - EOS visit date
    - Refusal date
    - Other date

Overall Survival (OS)

For each patient, we determined whether an OS event occurred and assigned the appropriate event date:

- **If a death date was recorded:**
    - The patient was classified as having an OS event (**OS_event = 1**).
    - The death date served as the OS event date (**OS_DATE**).
- **If no death date was recorded:**
    - The patient was considered censored (**OS_event = 0**).
    - The censoring date was defined as the earliest available follow-up date among:
        - Progression date
        - Refusal date
        - EOS visit date
        - Other date

2.2. Statistical Analysis

Kaplan–Meier curves were used to analyze the distributions of PFS and OS by treatment arm (experimental and control). Median survival estimates and survival probabilities at pre-specified time points were derived. Multivariable analyses were conducted using Cox proportional hazards models, adjusted for histology and disease type, with centre included as a random effect. The proportional hazards assumption was assessed using Schoenfeld residuals.

3. Results

3.1. Univariate Analysis

3.1.1 Progression-free survival (PFS)

The Kaplan-Meier curve for PFS (Figure 1a-b) shows the probability of patients remaining progression-free over time. The survival probabilities at key time points are shown in tables 1 and 2.

The Kaplan–Meier curves compare progression-free survival (PFS) between the control arm (blue) and experimental arm (red) over 18 months and, separately, extended follow-up to 60 months. Across both time horizons, the experimental arm shows a numerically higher PFS probability than the control arm after the early follow-up period, but the overall difference between curves is not statistically significant (log-rank p = 0.15). The 60-month plot primarily confirms that most progression events occur within the first ~18–24 months and that interpretation of any late differences should be cautious because the number at risk becomes very small (approaching zero beyond ~24–30 months).

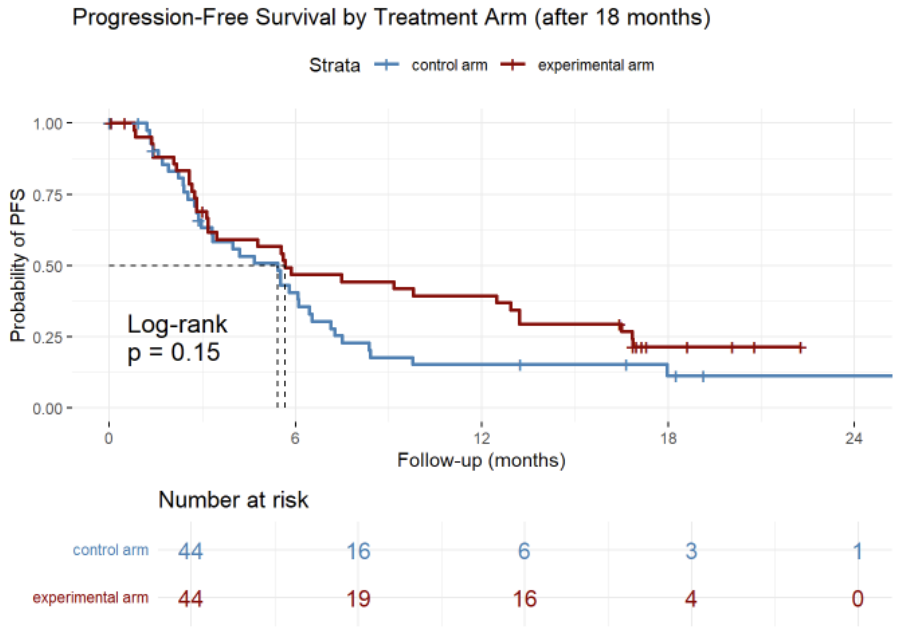

Figure 1a. The Kaplan–Meier curves compare progression-free survival (PFS) between the control arm (blue) and experimental arm (red) after 18 months

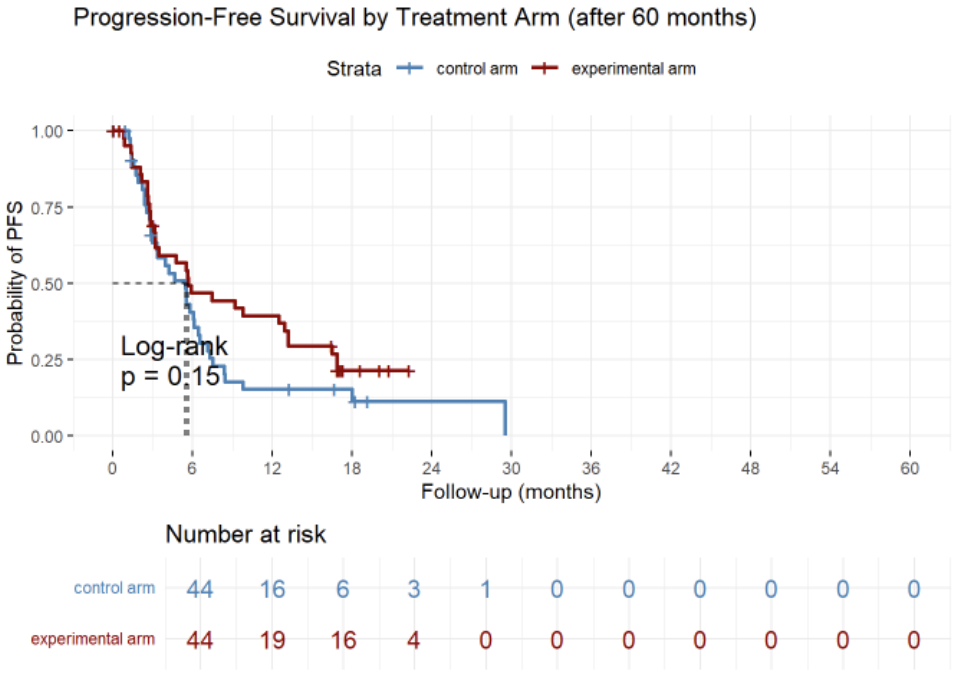

Figure 1b. The Kaplan–Meier curves compare progression-free survival (PFS) between the control arm (blue) and experimental arm (red) after 60 months

The tables (tables 1 and 2) summarize the Kaplan–Meier PFS estimates at predefined landmark times, reporting (i) the number of patients still at risk, (ii) the number of events occurring in the interval, and (iii) the estimated PFS probability with 95% confidence intervals (CIs). In the control arm, PFS declines from 100% at baseline to 40.6% at 6 months, 15.2% at 12 months, and 11.4% at 18–24 months (with widening CIs as the at-risk population becomes small). In the experimental arm, PFS is 46.9% at 6 months and 39.5% at 12 months (with corresponding 95% CIs). ***The experimental arm shows a consistent numerical trend toward higher PFS than the control arm, but the between-arm difference is not statistically significant by log-rank testing (p = 0.15),*** and precision is limited at later time points due to small numbers at risk.

Table 1. Survival probabilities and risk table for PFS model (control arm)

Time (months)	Patients at risk	Events	Survival Probability (95% CI)
0	44	0	100.0 (100.0 – 100.0)
6	16	24	40.6 (27.9 – 59.1)
12	6	10	15.2 (7.3 – 31.8)
18	3	1	11.4 (4.5 – 28.9)
24	1	0	11.4 (4.5 – 28.9)

Table 2. Survival probabilities and risk table for PFS model (experimental arm)

Time (months)	Patients at risk	Events	Survival Probability (95% CI)
0	44	0	100.0 (100.0 – 100.0)
6	19	22	46.9 (33.8 – 64.9)
12	16	3	39.5 (27.0 – 57.7)

18	4	7	21.5 (11.9 – 39.0)

3.2. Overall survival (OS)

The Kaplan–Meier overall survival (OS) analysis compares time-to-death between the control arm (blue) and experimental arm (red) from baseline through extended follow-up to 60 months, with tick marks indicating censoring and the risk table showing the shrinking number of patients still under observation over time (44 per arm at baseline) (figure 2). In table 3-4, ***the experimental arm demonstrates a consistent numerical trend toward higher OS than the control arm across landmark time points (e.g., 6 months: 85.3% vs 76.9%; 12 months: 60.9% vs 51.1%; 24 months: 41.5% vs 23.2%), but the overall difference between survival curves is not statistically significant (log-rank p = 0.19).*** At later time points (≥30 months), the number at risk becomes very small, confidence intervals widen substantially, and estimates should be interpreted cautiously.

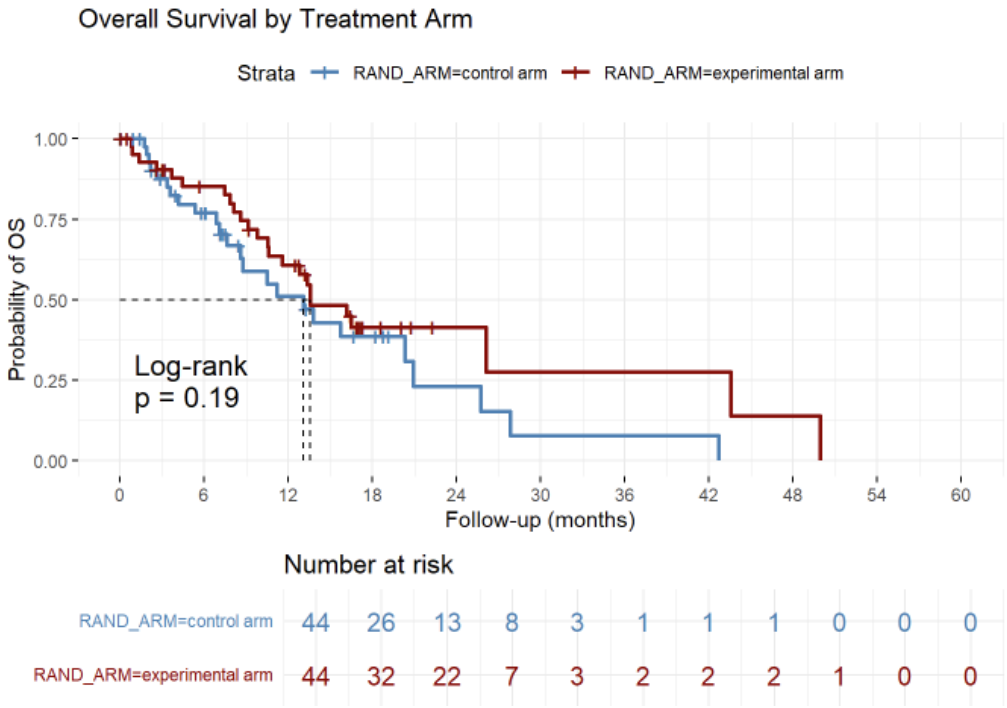

Figure 2. Kaplan–Meier overall survival (OS) analysis compares time-to-death between the control arm (blue) and experimental arm (red)

Table 3. Survival probabilities and risk table for OS model (control arm)

Time (months)	Patients at risk	Events	Survival Probability (95% CI)
0	44	0	100.0 (100.0 – 100.0)
6	26	9	76.9 (64.7 – 91.4)
12	13	7	51.1 (35.9 – 72.8)
18	8	3	38.6 (24.0 – 62.2)
24	3	2	23.2 (9.8 – 54.7)
30	1	2	7.7 (1.3 – 47.5)
36	1	0	7.7 (1.3 – 47.5)
42	1	0	7.7 (1.3 – 47.5)

Table 4. Survival probabilities and risk table for OS model (experimental arm)

Time (months)	Patients at risk	Events	Survival Probability (95% CI)
0	44	0	100.0 (100.0 – 100.0)
6	32	6	85.3 (75.1 – 96.9)
12	22	9	60.9 (47.2 – 78.6)
18	7	6	41.5 (27.8 – 62.1)
24	3	0	41.5 (27.8 – 62.1)
30	2	1	27.7 (11.3 – 67.8)
36	2	0	27.7 (11.3 – 67.8)
42	2	0	27.7 (11.3 – 67.8)
48	1	1	13.8 (2.7 – 72.1)

3.2. Multivariate Cox Model with Random Effects

To quantify the treatment effect on progression-free survival (PFS; Figures 3a–c) and overall survival (OS; Figures 4a–c) while accounting for cohort heterogeneity and potential confounding, we fitted a multivariate Cox proportional hazards model with a random effect. The model estimated the treatment hazard ratio adjusted for histology (adenocarcinoma, squamous cell carcinoma, other), disease type (oligometastatic vs poly-metastatic), and sex (female vs male). Consistent with the Kaplan–Meier curves, adenocarcinoma was associated with more promising PFS/OS than squamous cell carcinoma and the small "other" subgroup, and oligometastatic disease showed more promising PFS/OS than poly-metastatic disease, whereas differences by sex were less pronounced. After adjustment for these prognostic factors, the experimental arm was associated with a lower hazard of PFS with an adjusted hazard ratio of 0.66 (95% CI: 0.40 – 1.08), although not statistically significant (p = 0.096).

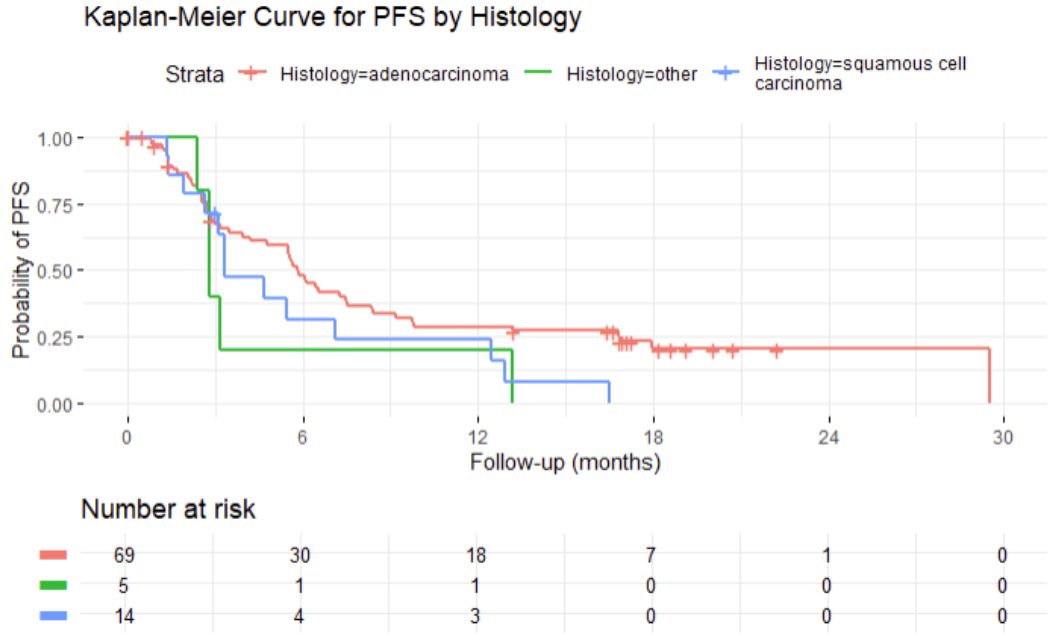

Figure 3a. Kaplan–Meier curve for PFS stratified by histology (adenocarcinoma=red vs squamous cell carcinoma=blue vs other=green).

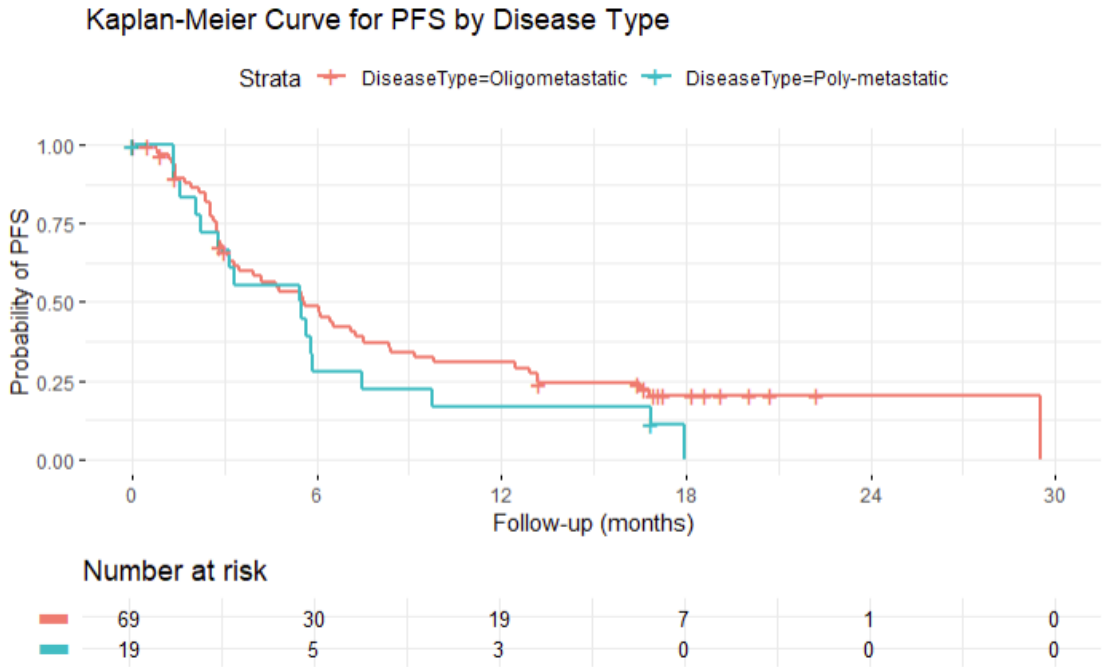

Figure 3b. Kaplan–Meier curve for PFS stratified by disease type (oligometastatic vs poly-metastatic).

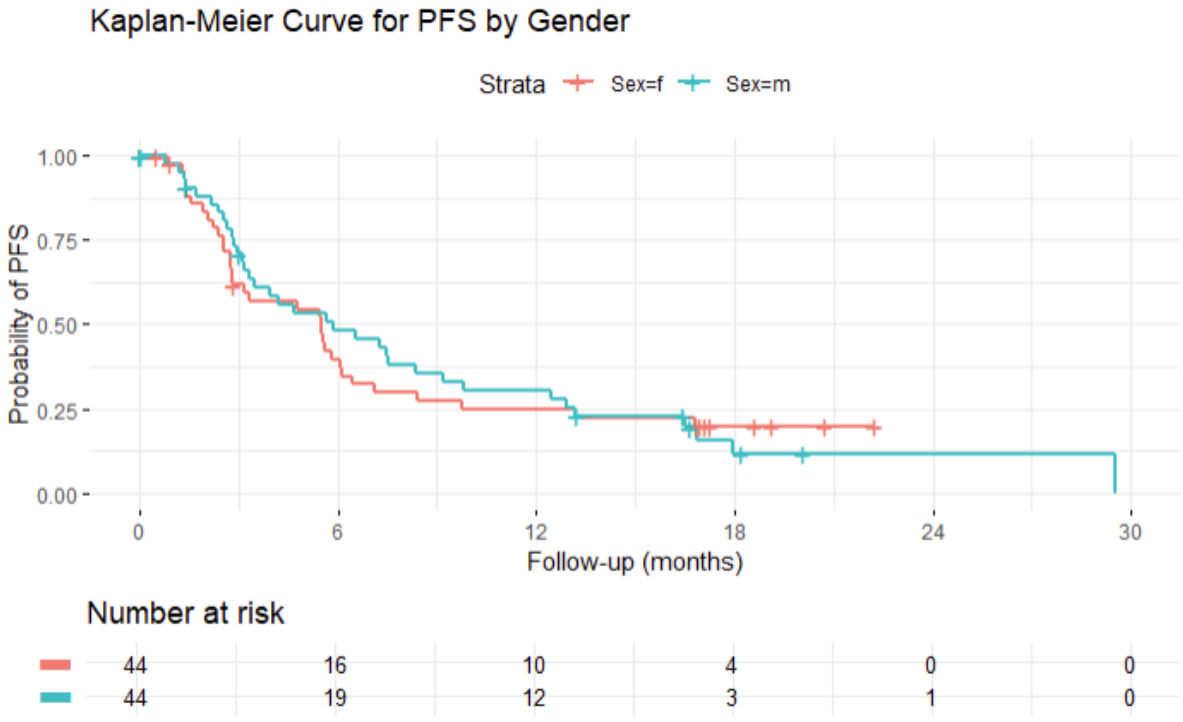

Figure 3c. Kaplan–Meier curve for PFS stratified by sex (female vs male).

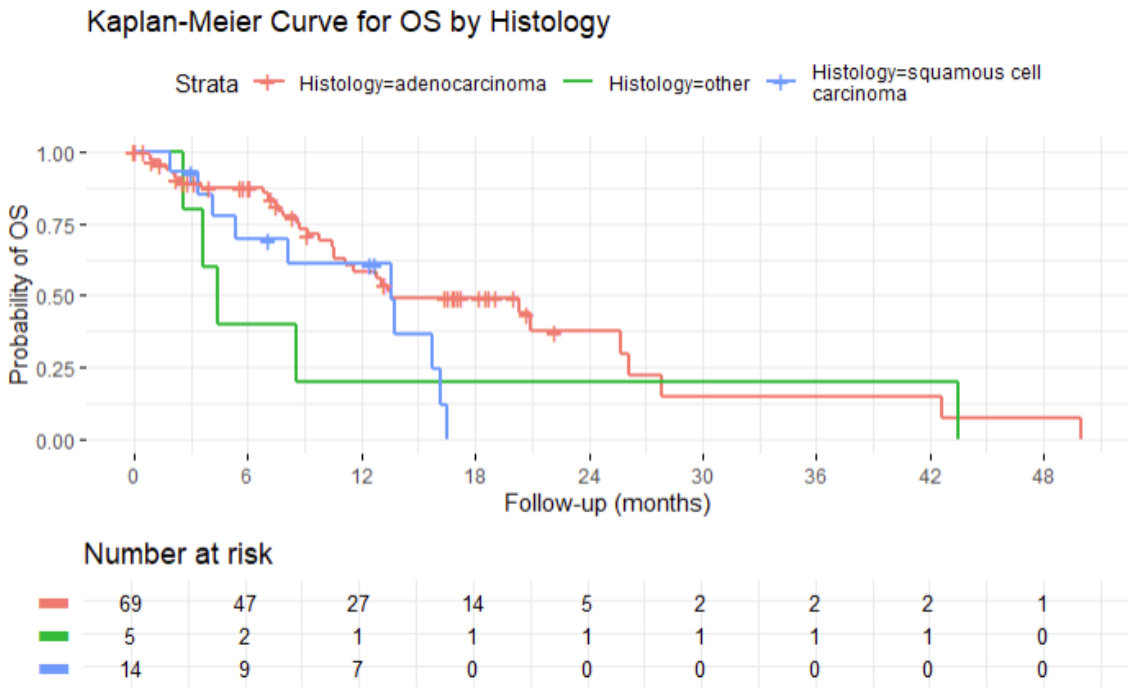

Figure 4a. Kaplan–Meier curve for OS stratified by histology (adenocarcinoma=red vs squamous cell carcinoma=blue vs other=green

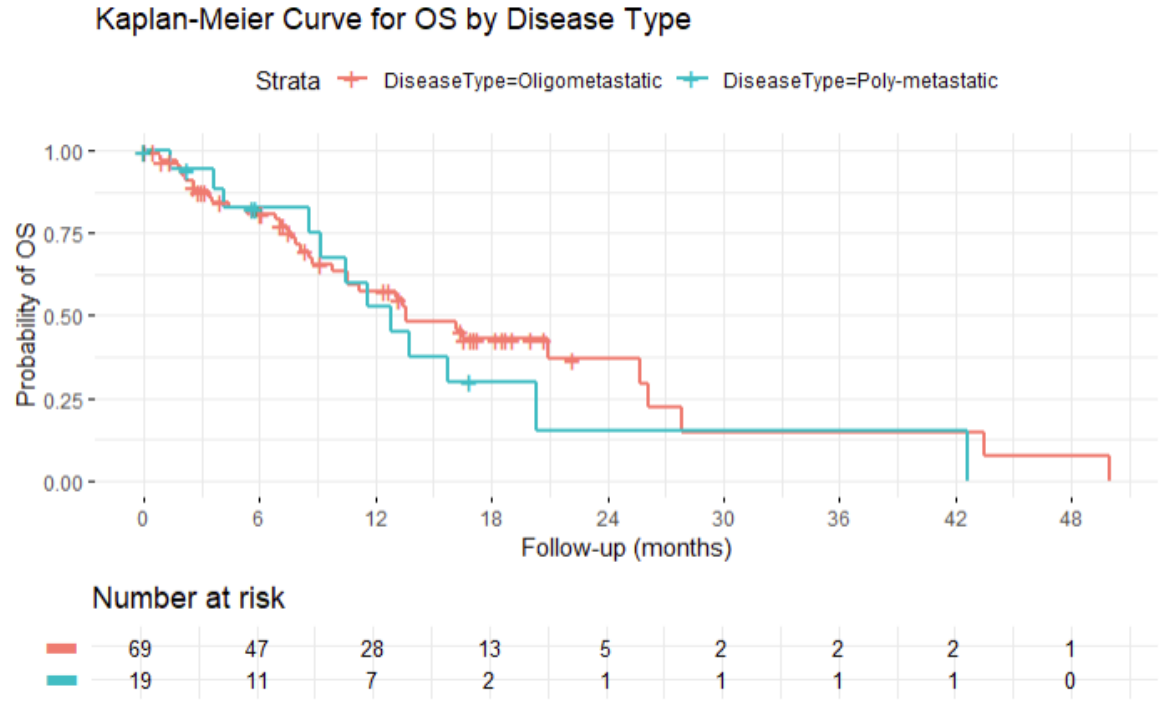

Figure 4b. Kaplan–Meier curve for OS stratified by disease type (oligometastatic vs poly-metastatic).

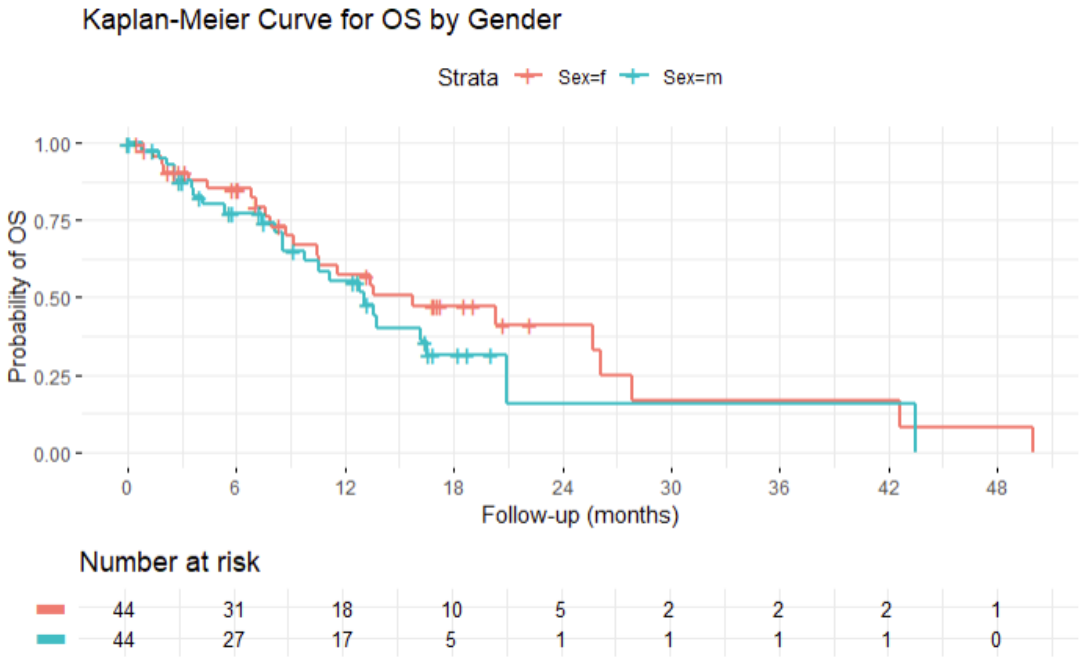

Figure 4c. Kaplan–Meier curve for OS stratified by sex (female vs male).

1. **Schoenfeld residuals**

As a final step, Schoenfeld residuals (figure 5a-b) were examined to assess the Cox model's proportional hazards assumption, namely that the effects of treatment and covariates (hazard ratios) are approximately constant throughout follow-up. Analyses of Schoenfeld residuals did not yield evidence of violation of the proportional hazards assumption (p values non-significant, figure 5a: p = 0.3483 and figure 5b: p = 0.214), meaning that the hazard ratios resulting from the regression modelling are valid over the complete follow-up time.

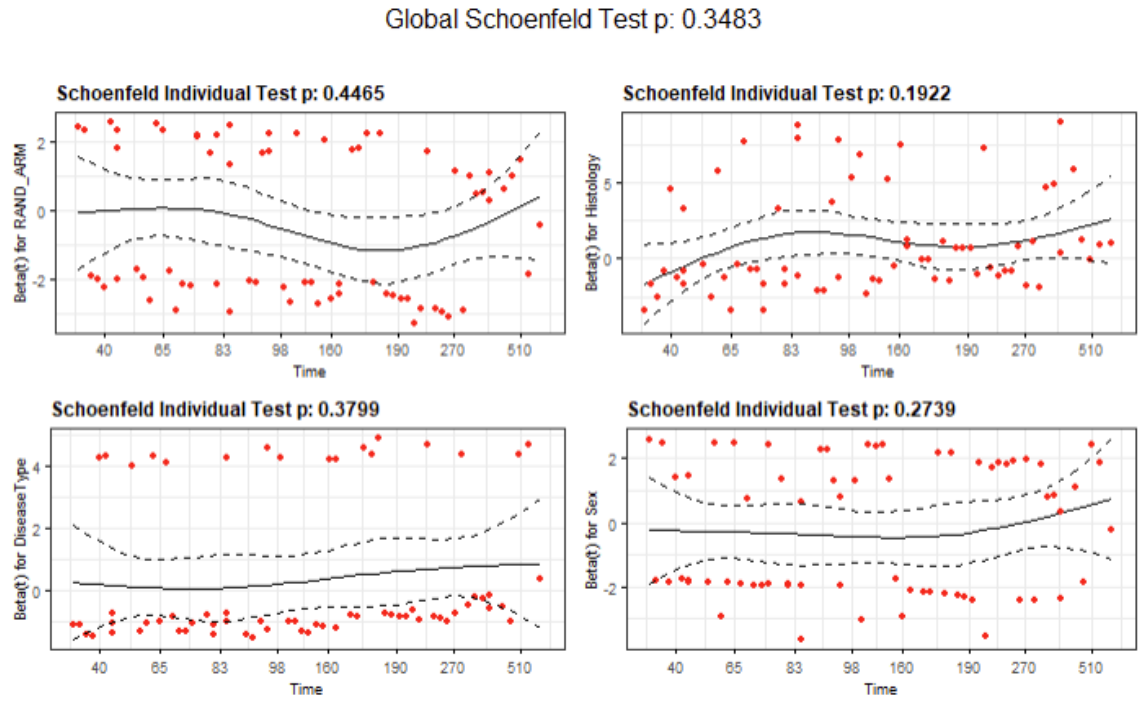

Figure 5a. Global Schoenfeld residual plot assessing proportional hazards for the multivariate Cox model (PFS).

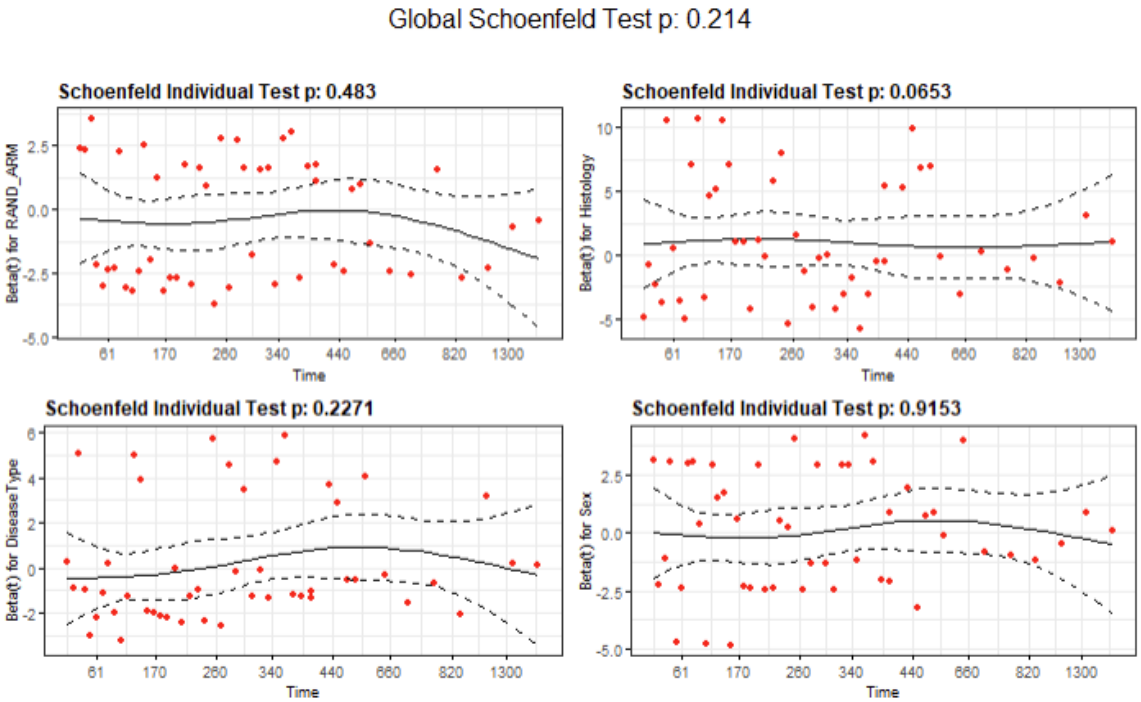

Figure 5b. Global Schoenfeld residual plot assessing proportional hazards for the multivariate Cox model (OS).

2. Overall conclusion on primary outcomes

Although the experimental arm demonstrates consistently more favorable PFS and OS trends than the control arm across the Kaplan–Meier curves and landmark estimates, the between-arm differences do not reach statistical significance in either the unadjusted (log-rank) comparisons or the adjusted Cox regression analyses. One plausible explanation is that the limited number of enrolled participants (and corresponding events) reduced statistical power, thereby increasing the likelihood of failing to detect a true between-arm difference. In other words, the trial may have been underpowered to demonstrate a statistically significant treatment effect, even if one exists. Whether these findings are sufficiently encouraging to justify initiating a well-powered, randomized phase III trial remains open to debate. Further analyses should evaluate whether predictive biomarkers can be identified to enrich for patients more likely to benefit from the experimental treatment.