

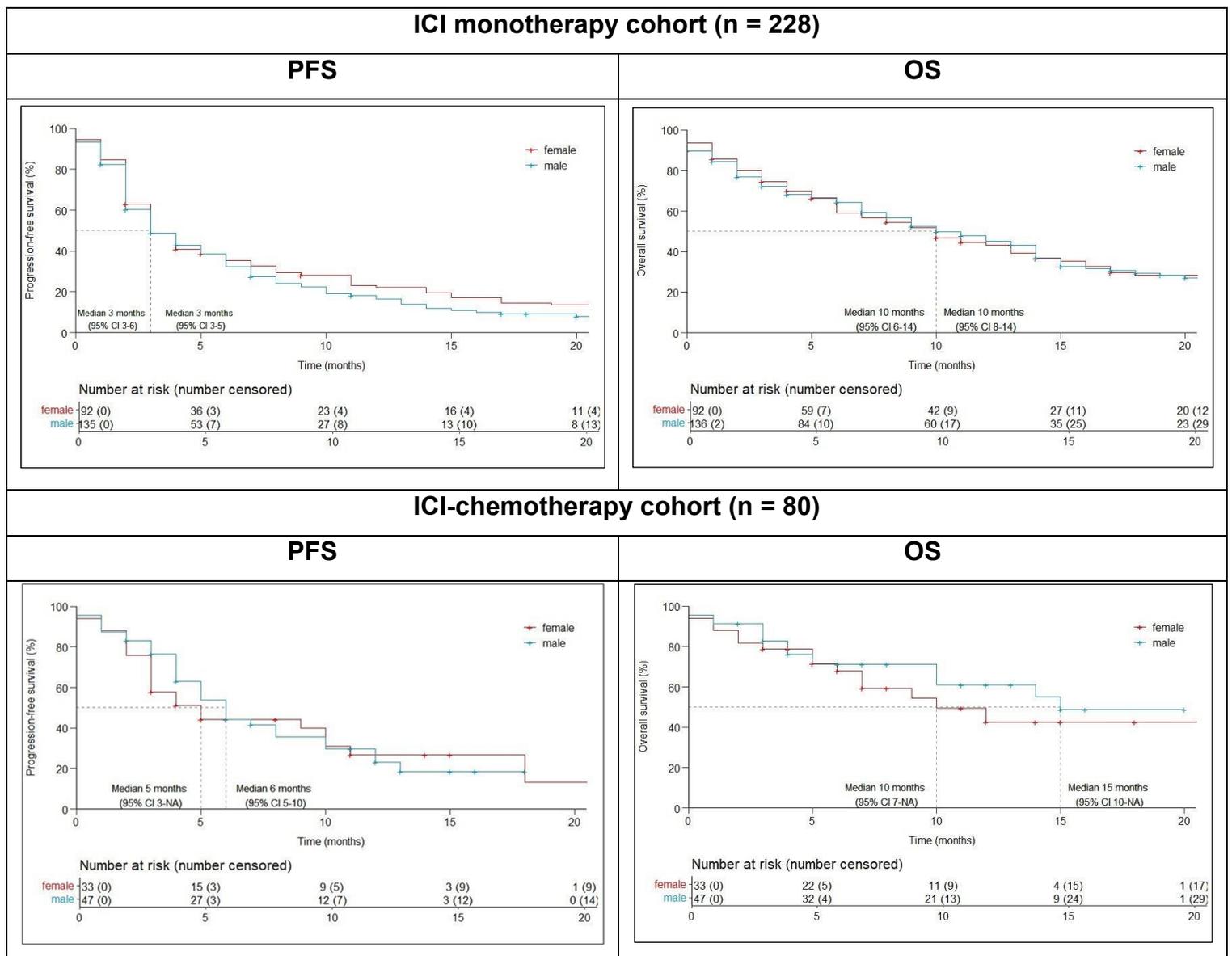
Supplementary analysis S1. Statistical approach to the impact of numeric differences between men and women on progression-free and overall survival (PFS/OS)

Problem: The ratio between male and female patients is unequal, which may have influenced PFS and OS.

Question: Would PFS and OS change, if the ratio was equal?

Results as presented in the original analysis:

| cohort | analysis | n | n female | Median (95% CI) female vs. male | p-value (log rank) |
|------------------|----------|-----|------------|---------------------------------|--------------------|
| ICI monotherapy | PFS | 228 | 92 (40.4%) | 3M (3-6) vs. 3M (3-5) | 0.273 |
| | OS | 228 | 92 (40.4%) | 10M (6-14) vs. 10M (8-14) | 0.592 |
| ICI-chemotherapy | PFS | 80 | 33 (41.3%) | 5M (3-NA) vs. 6M (5-10) | 0.780 |
| | OS | 80 | 33 (41.3%) | 10M (7-NA) vs. 15M (10-NA) | 0.398 |



Solution: Extension of the current female patient datasets with simulated data.

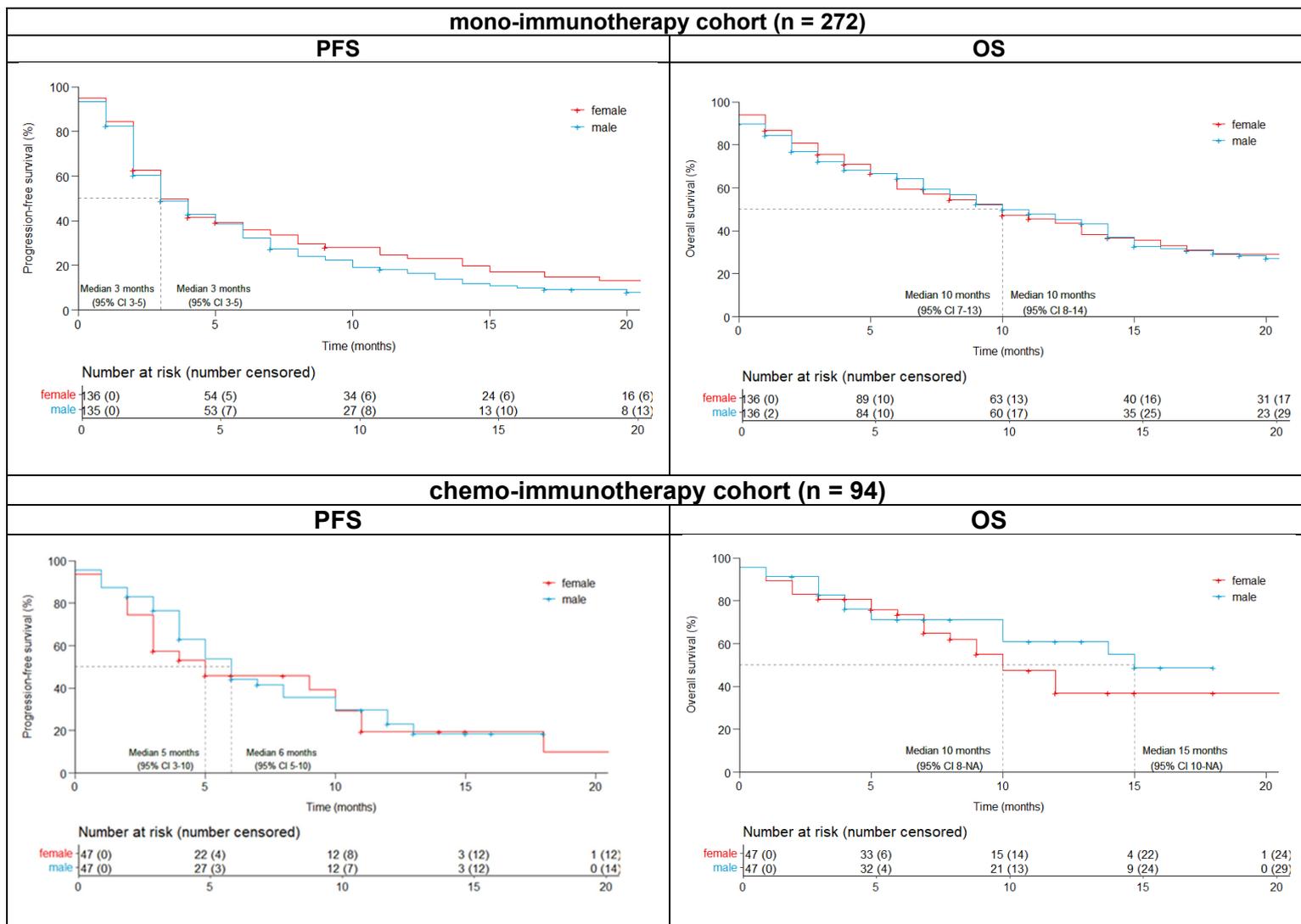
Methods: The aim is to derive cohorts with a balanced male-to-female-ratio. Therefore, the male population is fixed in both datasets, and based on the key characteristics of the existing female patients, additional female cases are simulated using the "survsim" package in R (R: A Language and Environment for Statistical Computing; Version 3.6.0; <https://www.R-project.org>). The simulated cases are added to the original datasets:

ICI-monotherapy cohort: 44 female subjects

ICI-chemotherapy cohort: 14 female subjects

Results with additional simulated data:

| cohort | analysis | n | n female | Median (95% CI) female vs. male | p-value (log rank) |
|------------------|----------|-----|-------------|---------------------------------|--------------------|
| ICI monotherapy | PFS | 272 | 136 (50.0%) | 3M (3-5) vs. 3M (3-5) | 0.241 |
| | OS | 272 | 136 (50.0%) | 10M (7-13) vs. 10M (8-14) | 0.660 |
| ICI-chemotherapy | PFS | 94 | 47 (50.0%) | 5M (3-10) vs. 6M (5-10) | 0.422 |
| | OS | 94 | 47 (50.0%) | 10M (9-NA) vs. 15M (10-NA) | 0.231 |



Conclusion: Simulation of a numerically balanced sex ratio in both therapy cohorts does not substantially alter PFS and OS outcomes.