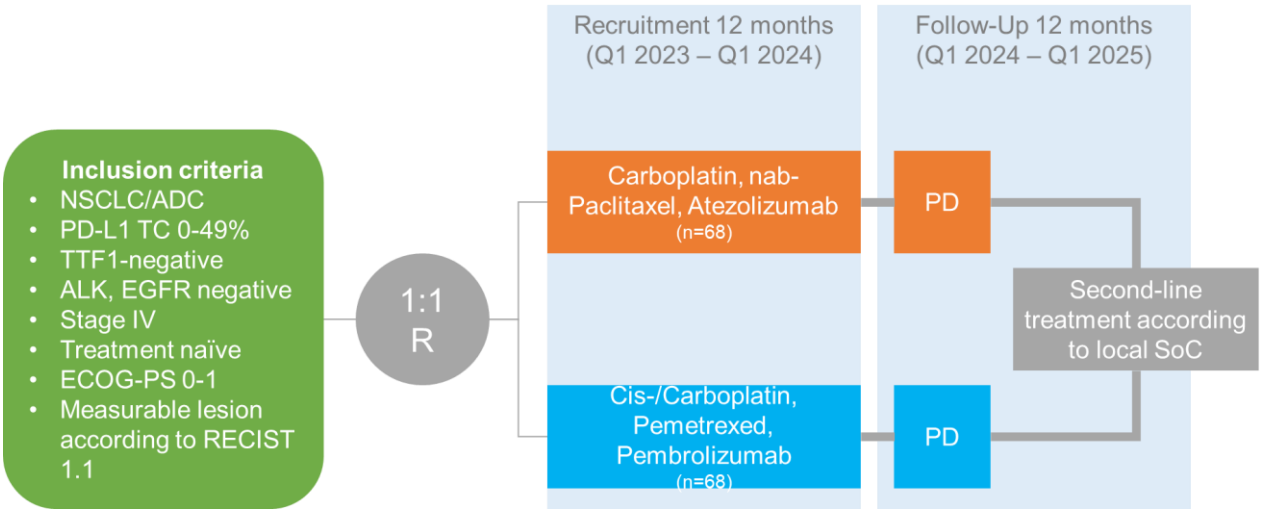
	known prognostic factors using propensity-score matching in a non-randomized setting [2]. A worse therapeutic response to pemetrexed-based regimens may be attributed to a type of adenocarcinoma mimicking the clinical features and behavior of squamous cell carcinoma [3-5]. Thus, incorporation of this biomarker may be helpful when choosing an appropriate therapy regimen. Currently patients with PD-L1 expression < 50% will receive checkpoint inhibitors combined with a platinum-based chemotherapy. Given the results of recent phase 3 studies, there is a choice between pemetrexed- and (nab-) paclitaxel-based regimens. Given a positive correlation between PD-L1 expression levels and response to checkpoint inhibitors the importance of the chemotherapy backbone increases with no or low PD-L1 expression. Hence, we hypothesize that patients with TTF-1 negative lung adenocarcinoma have superior overall survival with pemetrexed-free first-line immunochemotherapy [2].
SAMPLE SIZE ESTIMATION	Approximately 50% out of 45.000 patients with a newly diagnosed lung cancer/year are treated in certified lung cancer centers. Given the prevalence of stage IV in Germany (45%), lung adenocarcinoma (40%), TTF-1 negativity (25%), PD-L1 expression <50% (66%), actionable driver mutations (ALK, EGFR, ROS1; prevalence in TTF1-negative LuAD estimated to range between 2-3%) and an ECOG-PS 0-1 (60%) 780 (all patients) and 390 patients (treated in a certified lung cancer center) would potentially be eligible for the trial within a one year-period, respectively. Based on a hazard ratio of 0.546 (carboplatin AUC5-6 d1, nab-paclitaxel 100 mg/m2 d1,8,15, atezolizumab 1200 mg d1 q3w vs. cisplatin 75 mg/m2 or carboplatin AUC5-6 (according to investigator's choice), pemetrexed 500 mg/m2, pembrolizumab 200 mg; d1 q3w), it is required to observe 87 OS events, with the recruitment of 136 (68:68 per arm) patients with an allocation ratio of 1:1 (IMpower 130 vs. KEYNOTE-189). These calculations assume that the OS time follows an exponential distribution, using a two-sided log-rank-test with 2-sided 5% level of significance, 80% power, with 12-months recruitment and 12 months follow-up periods and 10% drop-out. The event rates will be monitored annually by the independent data monitoring committee to ensure the baseline assumptions are appropriate.
PARTICIPATING SITES	30

2. Trial Design



carboplatin AUC5-6 d1, nab-paclitaxel 100 mg/m2 d1,8,15, atezolizumab 1200 mg d1; q22
cisplatin 75 mg/m2 or carboplatin AUC5-6 (according to investigator's choice), pemetrexed 500 mg/m2, pembrolizumab 200 mg; d1 q22
maintenance treatment according to the chosen protocol (atezolizumab 1200 mg d1 q22 OR pemetrexed 500 mg/m2, pembrolizumab 200 mg; d1 q22

Treatment will be performed within the established standard of care. Both schedules are approved for metastatic lung adenocarcinoma in Germany.

3. References

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4. Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
CNS	central nervous system
CTCAE	common toxicity criteria of adverse events
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
ILD	interstitial lung disease
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association classification
ORR	objective response rate
OS	overall survival
PD-L1	programmed death ligand 1
PFS	progression-free survival
PS	performance status
RECIST	response evaluation criteria in solid tumors
TPS	tumor proportion score
TTF-1	Thyroid transcription factor 1