Background
Chemotherapy-induced toxicities frequently occur in non-small cell lung cancer (NSCLC) patients treated with platinum-based chemotherapy. Low skeletal muscle mass (SMM) has been associated with a higher incidence of (dose-limiting) toxicities.

Aim
To evaluate the association between skeletal muscle measures and chemotherapy-induced toxicity in a large cohort of NSCLC patients.

Methods
Design: Multicenter prospective follow-up study (PGXLUNG study). Patients: Diagnosed with NSCLC (stage II-IV), treated with first-line platinum-based (cisplatin or carboplatin) chemotherapy with pre-treatment imaging being available. Skeletal muscle measures: Skeletal muscle area (SMA) segmentation on pre-treatment abdominal imaging at the level of the third lumbar vertebra (L3), defined as skeletal muscle mass (SMM) and skeletal muscle density (SMD), see Figure 1. Outcome: Chemotherapy-induced toxicity (CTCAE 4.03) was categorized into: - Haematological toxicity (anaemia, leukocytopenia, neutropenia, thrombocytopenia); - Non-haematological toxicity (nephrotoxicity, neurotoxicity, esophagitis); - Dose-limiting toxicity (DLT; treatment switch, delay, de-escalation, discontinuation or hospitalization due to chemotherapy-induced side effects).

Results
- 297 patients were included, 36.6% (n=108) experienced at least once any haematological toxicity grade 3/4, 24.6% (n=73) any non-haematological toxicity grade ≥2, and 55.6% (n=165) any DLT, see Figure 2.
- Low SMM (ORadj 2.4, 95%CI 1.3-4.5) and age at diagnosis >65 years (ORadj 1.8, 95%CI 1.1-2.9) were statistically significantly associated with chemotherapy-induced overall haematological toxicity grade 3/4.
- Low SMM (ORadj 2.2, 95%CI 1.2-4.0) and high SMD (ORadj 0.4, 95%CI 0.2-0.7) were statistically significantly associated with a higher respectively lower risk of DLT.

Conclusions
NSCLC patients with pretreatment low skeletal muscle mass are at significantly higher risk for chemotherapy-induced haematological toxicities grade 3/4 and DLT.

Potential clinical relevance
Pretreatment evaluation of skeletal muscle mass may provide opportunities for tailored therapy and preventive strategies for chemotherapy-induced toxicity and could have a significant impact on clinical care.

Figure 1. Example of segmentation of skeletal muscle tissue at the level of the third lumbar vertebra (L3). Left: Unsegmented skeletal muscle tissue. Right: Segmented skeletal muscle tissue (red).

Figure 2. Chemotherapy-induced toxicity stratified by low, intermediate and high SMM and SMD status. Composite endpoints: overall haematological toxicity grade 3/4 scored using CTCAE: anaemia OR leukocytopenia OR neutropenia OR thrombocytopenia; overall non-haematological toxicity CTCAE grade ≥2 scored using CTCAE: nephrotoxicity OR neurotoxicity OR esophagitis; overall dose-limiting toxicity: switching treatment (cisplatin to carboplatin) OR treatment delay (>27 days) OR treatment de-escalation (<25%); OR treatment termination OR treatment-related hospitalization. A. Overall haematological toxicity stratified by SMM status. B. Overall non-haematological toxicity stratified by SMM status. C. Overall DLT stratified by SMD status. D. Overall DLT stratified by SMD status. E. Overall non-haematological toxicity stratified by SMD status. F. Overall DLT stratified by SMD status. Abbreviations: DLT: dose-limiting toxicity; ns: not statistically significant; SMD: skeletal muscle density; SMM: skeletal muscle mass. *p<0.05, Pearson Chi-square test.