
Article:
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Overall survival following heterogeneous FDG-guided dose-escalation for locally advanced NSCLC in the international phase III NARLAL2 trial

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Background:
The survival and loco-regional control for patients (pts) with locally advanced non-small cell lung cancer (LA_NSCLC) treated with radiotherapy (RT) are dismal despite adjuvant Durvalumab. However, there have been concerns about dose escalation for these pts since the unexpected result of the dose-escalation trial RTOG0617. A novel approach is therefore warranted to escalate the dose to the tumor. A possible approach is to use the principle from stereotactic body radiotherapy (SBRT) with inhomogeneous dose distribution. SBRT has demonstrated excellent local control in early-stage lung cancer. The international multicenter NARLAL2 (novel approach to RT for LA_NSCLC) phase III trial on dose escalation, randomized pts with LA_NSCLC between standard 66 Gy/ 33 fractions (F) versus heterogeneous FDG-PET driven dose escalation, aiming at mean dose to GTV-tumor$_{PET}$ 95 Gy/ 33 F and mean dose to GTV-node$_{PET}$ 74 Gy/ 33 F while strictly respecting dose to organs at risk. We here present the data on overall survival (OS) 1 year after the end of recruitment.

Methods:
Pts aged ≥18 years with LA_NSCLC were recruited from seven institutions in Denmark and Norway. Eligibility criteria included ECOG PS 0-1, histological or cytological confirmed NSCLC stage IIB-IIIB, signed informed consent, and a clinically acceptable plan for RT with conventional 66 Gy/ 33 F. PET-CT and brain MR were part of staging. Pts were randomly assigned to either treatment group (1:1, stratified for center and histology). The trial aimed to have iso-lung toxicity within the treatment arms by creating two RT plans (before randomization) for each patient (one for each treatment arm) with matching mean lung dose and lung V_{20Gy}. The follow-up (FU) were scheduled weekly during RT, every 3rd month for 2 years, and every 6th month for another 3 years after randomization. At FU visit a CT-scan and toxicity scoring were performed. All interim analyses were passed without

interventions (toxicity and OS). The trial's primary endpoint was time to loco-regional failure from randomization. Secondary endpoints included OS, acute, and late toxicity. The sample size calculations requested 350 pts to be enrolled in the study. Recruitment of the pre-planned number of pts finalized in March 2023. The trial was registered with ClinicalTrials.gov (NCT02354274).

Results:
From January 2015 to March 2023, 350 pts were randomized: 177 and 173 pts in standard and escalated arms respectively. The two groups were well-balanced regarding age, gender, stage, and PS. The dose to GTV-tumor was 66.5 Gy [66.2, 67.1] (median [IQR]) in the standard arm and 88.1 Gy [84.9, 90.4] in the escalated arm. Median OS were 35.8 months (m) and 51.6 m for pts treated in the standard and escalated arm, respectively (*p = 0.36*). Median FU time 50.8 m (reverse Kaplan-Meier).

Conclusions:
Dose escalation is safe in the NARLAL2 setting with respect to OS. Clinical trial information: NCT02354274.