Conference abstract:
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patients experienced grade 2 pneumonitis and one (3.2%) with grade 3. No grade 4 or 5 toxicity. Simulated radiotherapy plans indicated GTVp, GTVn, and PTV after the first 2-cycle immunotherapy significantly ($P<0.001$) decreased by 35.7 cm^3 (45.0% reduction), 10.7 cm^3 (39.1% reduction), and 84.5 cm^3 (25.1% reduction), respectively. The mean lung dose, lung V5, V20 and V30 significantly reduced by 1.2 Gy (8.0% reduction, $P<0.001$), 4.6% (8.1% reduction, $P<0.001$), 1.8% (7.7% reduction, $P=0.002$) and 1.6% (9.8% reduction, $P=0.002$), respectively. **Conclusions:** Two cycles of induction chemo-immunotherapy followed by definitive CRT for large-volume LA-NSCLC is feasible, with promising tumor control and significant target volume reduction. Further investigations on this novel regimen and optimal patient selection are warranted. **Keywords:** Immunotherapy, Non-small-cell lung cancer, Chemoradiotherapy

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Impact of Antibiotic Use Before Definitive Concurrent Chemoradiation in Patients With Locally Advanced Non Small Cell Lung Cancer

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Introduction: The study evaluated whether antibiotic treatment before chemoradiotherapy influenced outcomes in patients with locally advanced non-small cell lung cancer (LA-NSCLC). **Methods:** The records of LA-NSCLC patients treated with chemoradiotherapy between 2010 and 2017 at West China Hospital were retrospectively examined together with their antibiotic use (antibiotic type, duration of treatment, and time between discontinuation and chemoradiotherapy). The influence of antibiotics on progression-free survival (PFS) and overall survival (OS) was evaluated with Kaplan-Meier curves and univariate and multivariate Cox regression. **Results:** Of 522 patients, 176 had received intravenous broad-spectrum antibiotics in the month before chemoradiotherapy. Antibiotic use was linked to both reduced PFS (7.9 vs. 13.4 mo, $p<0.001$) and OS (20.4 vs. 25.3 mo, $p=0.049$). Multivariate regression demonstrated that antibiotic treatment was an unfavorable independent prognostic factor for LA-NSCLC patients that received chemoradiotherapy (HR, 1.234; 95% CI, 1.019-1.494; $p=0.031$). Prognosis was also influenced by the antibiotic type, length of treatment, and interval between discontinuation and start of chemoradiotherapy initiation. β-lactamase inhibitors were found to be the most harmful (median OS for β-lactamase inhibitors /Fluoroquinolones / Cephalosporins:16.5/19.9/25.9 mo, $p=0.045$). Cutoff values for interval and duration calculated by the X-tile procedure showed that intervals of 7-16 days or durations $\leq$6 days did not significantly affect OS relative to untreated patients (intervals: $p=0.9$, duration: $p=0.93$). **Conclusions:** Antibiotic treatment for longer than six days, especially with β-lactamase inhibitors, was associated with poor prognosis. Furthermore, delaying chemoradiotherapy for 7-16 days after antibiotic discontinuation may reduce these negative effects. **Keywords:** Non-small cell lung cancer, Antibiotic treatment, chemoradiotherapy

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Population Kinetic Assessment of Chemoradiation for Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Progression-free survival (PFS) curves generally approximate first order kinetics. PFS curve exponential decay nonlinear regression analysis (EDNLRA) provides useful insights. Chemoradiation is standard therapy in locally advanced NSCLC. Durvalumab improves PFS. **Methods:** Using PubMed, we identified trials published from 2010 to February 2022 using chemoradiation for locally advanced NSCLC. We used GraphPad Prism 7 for EDNLRA of digitized PFS curves. We excluded curves derived from fewer than 50 patients and curves that were less than 25 months long. We also excluded data from 3 outliers, although their inclusion would not alter our conclusions. **Results:** Across 54 evaluable curves, there was a median (range) of 96 (50-829) patients per curve, with curve length a median (range) of 60 (26-150) months. On 1-phase-decay EDNLRA, PFS half-life was a median (range) of 13.8 (7.2-25.9) months. Of the 54 curves, 53 fit 2-phase-decay EDNLRA models and demonstrated a rightward inflection on log-linear plots. Curve 2-phase decay indicated presence of a rapidly progressing subpopulation and a separate potentially cured subpopulation. The rapidly progressing subpopulation accounted for a median (range) of 86% (27%-95%) of the entire population, meaning that there was a potentially cured subpopulation of 14%. PFS half-life was 9.3 (4.0-15.7) months for the rapidly progressing subpopulation and was 3.4 x 10^{15} (35 to 6.1 x 10^{15}) months for the potentially cured subpopulation. (Since the half-life of the potentially cured subpopulation was generally much longer than the duration of follow-up, 95% confidence intervals for this half-life were very wide for most curves. Since PFS is impacted by death from any cause, we conclude that this overestimates the true PFS half-life for the favorable group). For patients who remained progression-free at different follow-up time points, EDNLRA data permitted estimation of the proportion who were still destined to eventually relapse. Of those still progression-free at 12, 24, 36, 48, 60 and 120 months, respectively, the estimated proportion destined to eventually relapse was 35%, 14%, 6%, 2%, 1% and 0.01%. Conversely, of those still progression-free at 36 and 60 months, respectively, 94% and 99% are probably cured. In the PACIFIC trial, the proportion of patients in the subpopulation with good outcome increased from 43% on the placebo arm to 74% on the durvalumab arm. PFS half-lives in the rapidly progressing subpopulation were similar on the durvalumab and placebo arms. This is in keeping with immune checkpoint inhibitors having either no effect or else a marked beneficial effect on different patients, as also seen in metastatic disease. PFS half-life in the favorable subpopulation was 61 months on the durvalumab arm vs 97 months on the placebo arm. This suggests that the durvalumab arm may eventually demonstrate 3-phase decay with longer follow-up (a rapidly progressing subpopulation, a subpopulation cured by chemoradiation and an intermediary subpopulation that is not cured but has prolonged control with durvalumab). **Conclusions:** Population kinetic assessments of PFS curves for patients with locally advanced NSCLC offer potentially useful biological and statistical insights. **Keywords:** chemoradiation, non-small cell lung cancer, population kinetics

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CONCORDE - A Phase Ib Platform Study of Novel Agents in COmbinatioN with COnventional RaDiothErapy in Non-small Cell Lung Cancer (NSCLC)

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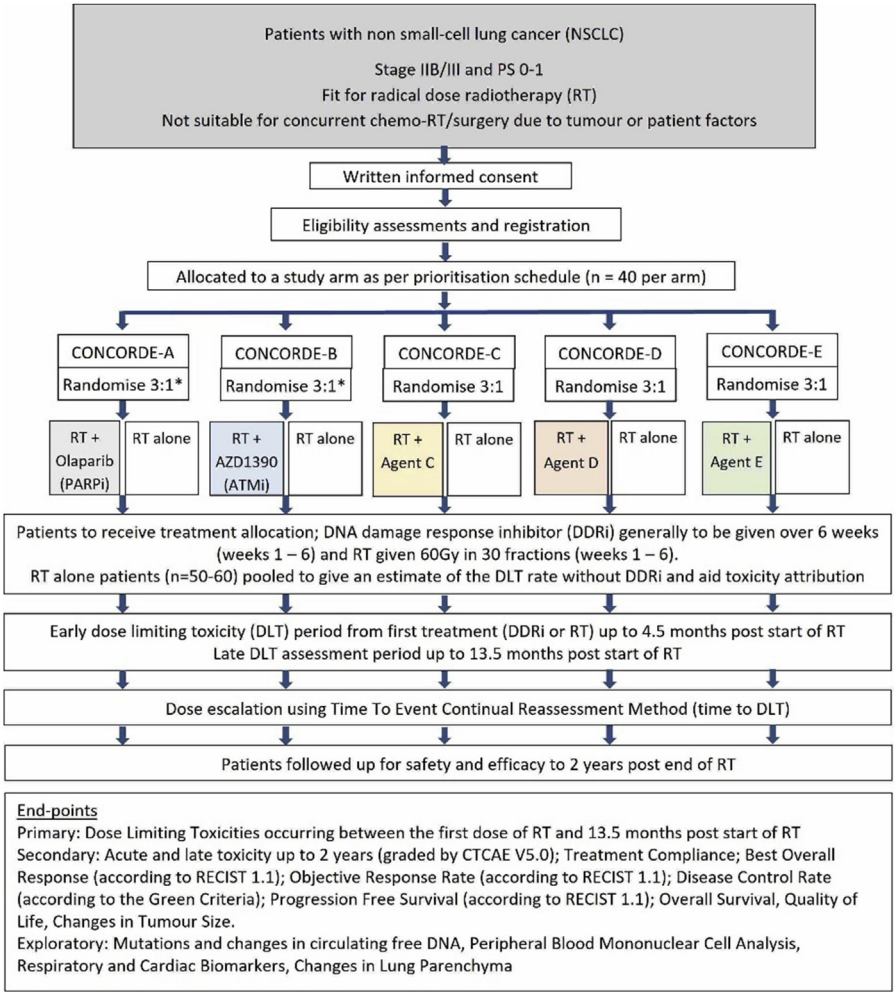

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Introduction: The CONCORDE study is sponsored by the University of Leeds and funded by Cancer Research UK and AstraZeneca. It is an innovative, hypothesis-driven open-label, randomised, phase Ib, multi-institution, platform study for patients with NSCLC receiving radical radiotherapy (RT). It aims to assess five DNA damage response inhibitors (DDRi) with participants randomised to receive one agent in combination with RT or RT alone. Two of the arms will also deliver Durvalumab and DDRi consolidation. CONCORDE adopts a Bayesian adaptive model-based approach to dose escalation. An estimated 210 patients will be recruited from 13 centres across the UK, including 30 patients in each experimental arm and approximately RT alone 50-60. The estimated total duration of trial: 6 years. **Methods:** Key eligibility: Stage IIB/IIIA/B/C NSCLC, medically inoperable and not suitable for concurrent chemo-radiotherapy, ECOG PS 0-1. Patients will be treated with radical RT given at a dose of 60Gy/30# delivered over 6 weeks. As per Figure 1, they will be allocated to one of 5 study arms as per prioritisation schedule (n=40 per arm). Within that arm they will be randomised to RT with or without DDRi (randomised 3:1). The primary endpoint is to assess the safety and determine the recommend phase II dose (RP2D) of each DDRi. The RP2D will be the dose level at which it is estimated 25% of subjects will experience dose limiting toxicity during and up to 13.5 months following RT. **Results:** Trial arms A (PARPi) and B12 (ATMi) are open to recruitment in 6 centres and 14 patients have been recruited (as of 15/03/2022). **Conclusions:** Further arms and centres to open soon. Correlative studies aiming to identify biomarkers of toxicity and response to combination therapy, and the impact of treatment on the immune system are in development. For further information go to: https://clinicaltrials.gov/ct2/show/NCT04550104 Trials unit contact: ctru_concorde@leeds.ac.uk **Keywords:** Radiotherapy, DNA damage response inhibitors, Phase 1b trial