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Title (150/150 characters)
ATM inhibition with AZD1390 and conventional radiotherapy in non-small cell lung cancer: interim report from the CONCORDE phase Ib trial (NCT04550104)

Purpose/Objective
The 'ataxia telangiectasia mutant' (ATM) kinase plays a central role in multiple DNA damage response (DDR) pathways, and DDR inhibitors (DDRIs) enhance the lethality of radiation for cancer cells in preclinical experiments. Early-phase clinical data in glioblastoma suggest the combination of ATM inhibitor AZD1390 with definitive radiotherapy (RT) is tolerable[1]. There is an unmet need for combining RT with novel drugs in NSCLC due to high locoregional relapse rates with standard treatment.

Material/Methods
CONCORDE is a multicentre, randomised, open-label, phase Ib platform trial[2] utilising an adaptive Bayesian model-based approach[3] to determine the recommended phase II dose of 4 DDRIs, including AZD1390 (**Figure 1**). Patients with unresectable stage IIB/III NSCLC planned for curative-intent RT (60Gy/30 fractions), KPS>70 but not suitable for concurrent chemotherapy were enrolled. Arm B patients were randomised 3:1 to receive either AZD1390 concurrently with RT, or RT–alone. The statistical design includes informal comparison with cross-platform RT–alone patients. The primary endpoint is the occurrence of dose limiting toxicities (DLTs). CONCORDE is funded by CRUK and AstraZeneca.

Results
Fourteen participants received AZD1390 plus RT, with equal numbers of squamous and adenocarcinomas. Eight were male (57%), median age 76 years (range 49–86) and FEV1pred 77% (range 48–112). DLTs, CTCAE G3+ and serious adverse events were observed in 4 (29%, all dose level 3), 10 (71%) and 9 (64%) participants respectively. Oesophagitis occurred in 9 participants (64%): grade 2 in 78%, grade 3 in 22%. Oesophagitis duration was prolonged (median 67 days, range 8–181), and 7 participants required morphine (50%). Median onset time was 2.4 weeks but late oesophageal events occurred in 3 participants (21%), including 1 without early toxicity. In the RT–alone arm (n=16), oesophagitis onset was identical (2.3 weeks), but duration was shorter (27 days) and fewer participants required morphine (5, 28%). Baseline characteristics and median oesophagus dose metrics were similar (experimental vs RT–alone: V60 0.50% vs 0.02%, V30 30% vs 25%). Experimental arm median PFS was 9.5 months (95%CI 5.4–13.3) (RT–alone 8.8 months (95%CI 4.4–13.3)).

Conclusion
AZD1390 was escalated to dose level 3 (40mg once-daily on RT days). Based on the observed oesophageal toxicity, the independent Safety Review Committee decided to close Arm B early. Analysis of patient-reported outcomes, efficacy outcomes and oesophagus-derived cfDNA are ongoing. Other Arms have been successfully escalated to dose levels 2 (C+E) or 3 (A) with integration of consolidation durvalumab in 2 arms (C+E) and recruitment continues.

Key Words (3/3 ‘words’ and 50/50 characters)

Platform trial, lung radiotherapy, radiosensitiser

References (718/750 characters)

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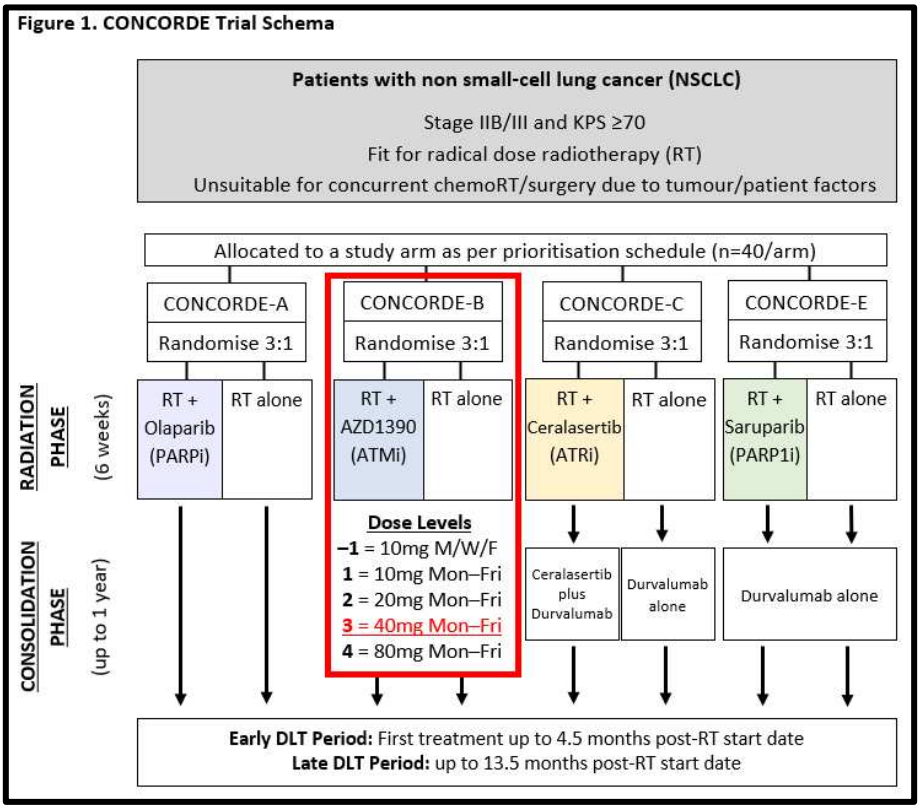

Figure 2. Swimmer's plot of oesophageal toxicity