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Modern era radical radiotherapy toxicity: a preliminary CONCORDE analysis of the calibration arm

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Topic

Clinical: Lung

Keywords

lung cancer, radiotherapy, toxicity

Purpose/Objective

CONCORDE is a UK-based phase Ib platform study whose primary aim is to assess dose limiting toxicities (DLTs) for DNA damage response inhibitors (DDRis) when prescribed alongside curative-intent radiotherapy(1,2). Participants not suitable for concurrent chemo-radiotherapy are randomised to receive either a DDRi +/- consolidation durvalumab in combination with radiotherapy (experimental arms) or to radiotherapy alone +/- consolidation durvalumab (calibration arm).

Few studies using contemporary radiotherapy either alone or in the sequential setting have reported in recent years. Therefore, a calibration arm, using modern radiotherapy techniques, is incorporated into the CONCORDE study to ensure the safety and toxicity data in the experimental combination arms are interpretable within the context of the current study. This data is required to account for improvements in radiotherapy techniques and quality assurance, aiding interpretation rather than permitting formal comparison between arms.

This preliminary analysis aims to describe radiotherapy data accumulated thus far and clinician assigned acute and late toxicity (with a focus on oesophagitis and pneumonitis) experienced by patients receiving radiotherapy

Primary objective: to assess the safety and determine the recommended phase II dose of each DDRi, based on the occurrence of DLTs, used in combination with radical thoracic radiotherapy for patients with locally advanced non-small cell lung cancer (NSCLC).

Key Eligibility: Inoperable stage IIB/IIIA-C NSCLC, not suitable for concurrent chemoradiotherapy with Karnofsky Performance Score≥70.

All patients receive 60Gy in 30 fractions over 6 weeks. State of the art radiotherapy planning and delivery is mandated (4DCT planning, fixed beam IMRT or VMAT, daily online CBCT with adaptation as required). See table 1 for dose constraints to the Organs at Risk.

Organ	Planning parameter	Dose constraint
Lungs (-GTV)	V20 Mean lung dose	≤30% 18Gy
Oesophagus	V50 Max dose 1cc	<33% 63Gy

Table 1: Dose constraints to the organs at risk

A secondary endpoint is the collection of acute and late toxicity up to 2 years post-radiotherapy as graded by CTCAE V5.0 and through patient reported outcome measures (PROMs). CTCAE toxicity is assessed weekly during radiotherapy, for a minimum of six weekly up to 6 months post-radiotherapy (6-, 12-, 18- and 24-weeks) and subsequently every three months (9-, 12-, 15-, 18-, 21- and 24-months). PROMs are also collected at baseline and at the end of radiotherapy, 3-, 6-, 12-, 18- and 24-months post-radiotherapy.

This preliminary analysis will describe toxicity experienced, the CTCAE grade, time of onset alongside radiotherapy planning data.

The study is sponsored by the University of Leeds and funded by Cancer Research UK and AstraZeneca.

Results

As of 15/10/2023, 65 patients have been registered in the study from 9 UK centres, of which 49 were randomised in one of 3 arms (CONCORDE-A olaparib, CONCORDE-B AZD1390 and CONCORDE-C ceralasertib with consolidation durvalumab). Of those randomised: 19 patients have or are currently receiving radiotherapy alone, of which 10 received induction chemotherapy.

The 13 radiotherapy alone patients who have completed the short DLT period (4.5 months post start of radiotherapy) will be the focus of this summary. 6 of these patients have also completed the long DLT period (13.5 months post start of radiotherapy).

Two patients experienced grade ≥2 pneumonitis (grade 2=1, grade 3=1) and 5 patients experienced grade ≥2 oesophagitis (all grade 2). No patients experienced significant pneumonitis and oesophagitis together. One patient who developed pneumonitis developed symptoms during radiotherapy and one following completion of radiotherapy. All patients who developed oesophagitis were recorded as developing it during radiotherapy.

Grade ≥2 pneumonitis	Yes	No	Yes	No	Yes	No	Yes
Number	2	11	2	11	2	11	2
Mean	12	64.83	81.66	17.86	25.89	11.10	14.74
SD	11.31	58.45	22.66	6.53	2.60	3.26	1.35
Min	4	15.72	65.64	10.75	24.05	6.92	13.78
Max	20	221.50	97.69	29.00	27.73	16.60	15.69

Table 1: Summarises radiotherapy statistics between those who experienced grade ≥2 pneumonitis and those who did not.

	Toxicity occurred (weeks from start of radiotherapy)	GTV volume (cm)		Oesophagus V50 (Gy)		Oesophagus max dose 1cc (Gy)	
Grade ≥2 oesophagitis	Yes	No	Yes	No	Yes	No	Yes
Number	5	8	5	8	5	8	5
Mean	3	90.15	31.04	12.19	12.50	43.19	48.03
SD	0.71	58.26	12.72	14.98	11.81	19.00	16.25
Min	2	25.56	15.72	0.00	0.00	17.18	28.30
Max	4	221.50	50.62	35.96	24.67	60.49	60.13

Table 2: Summarises radiotherapy statistics between those who experienced grade ≥2 oesophagitis and those who did not.

Conclusion

In this unplanned preliminary analysis, we report low rates of toxicity in patients who receive radical radiotherapy alone in the modern radiotherapy era. Despite small numbers and therefore difficult to draw meaningful conclusions a 7% risk of developing grade 3 pneumonitis is in keeping with figures previously quoted in the literature (3). On reviewing radiotherapy planning statistics, we observe that the patients who experienced more significant pneumonitis had greater GTV volume, lung V20 and mean lung doses. Furthermore patients who experienced more significant oesophagitis had higher oesophagus V50 and oesophagus max dose 1cc.

The integration of a calibration arm will continue to help the interpretation and attribution of toxicity in the experimental arms of the CONCORDE study. A more complete analysis will be performed on this cohort upon study completion with an opportunity to perform more in-depth analysis that includes patient, tumour and dosimetric factors, as well as considering radiosensitivity through the integration of exploratory data (including genomic, radiomic and cell-free DNA features) and PROMs.

For further trial information and rationale please see: https://clinicaltrials.gov/ct2/show/NCT04550104

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