Proton radiotherapy to improve non-small cell lung cancer outcomes: Clinical trial proposal

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Background
- There is limited supporting evidence for proton radiotherapy in non-small cell lung cancer (NSCLC)
- Thoracic proton radiotherapy research is required

Trial hypotheses
Proton CTRT will improve OS c.f. photon CTRT due to:
- Reduction in RT related cardiac toxicity
- Reduction in RT related lymphopenia
- Reduction in acute CTRT S/E → Increase in % of patients who initiate durvalumab

Phase II trial
Main patient eligibility:
- Stage III NSCLC
- Suitable for CTRT & adjuvant durvalumab (PS 0-1)

Before cCRT
Proton RT + chemo (IMPT)  photon RT + chemo (IMRT)

During cCRT
Chemoradiotherapy

Adjuvant durvalumab (within 42 d)
(if radiological response on CT and no grade ≥2 adverse-events)

Baseline biomarkers:
(1) Cardiac risk assessment
(2) Blood biomarkers (cardiac, cf-DNA & immune)
(3) 1x cardiac MRI; appx 45 min

RT dose in both arms: 60Gy (RBE) in 30Fx

Biomarkers during cCRT:
(1) Blood biomarkers @ w3

Biomarkers after cCRT:
(1) Blood biomarkers after completion of cCRT + 6m & 12m
(2) 1x cardiac MRI & PFTs → 6m

Trial endpoints
Co-primary endpoints: OS & health-related quality of life
Safety and efficacy: IDMC annually to ensure safety & efficacy of proton CTRT
Pre-planned secondary endpoints:
- % of patients who initiate adjuvant durvalumab (composite of toxicity & tumour control) & durvalumab dose intensity
- % of patients with significant cardiac MRI changes at 6m
- % of patients with significant pulmonary function test changes at 6m
- % of patients who develop CTCAE v5.0 grade ≥3 lymphopenia @ w3 and/or post CTRT

Key messages
- Comparative proton vs photon RT lung studies needed
- Trial will address a # of unmet clinical needs + provide radiobiology insights into proton RT
- Many trial development tasks on-going (e.g. consumer input, modelling of likely survival gains with protons)

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