UK Clinical trial update

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Lung SABR Trials

• Stage I Disease
• Oligometastases
• Oligoprogression
• Advanced Metastatic Disease
Stage I Disease

• Peripheral Stage I
  • Higher risk for resection – SABRtooth
• Central Stage I
  • LUNGTECH
• Versus Conventional RT
  • SPACE Trial
Peripheral Lung SABR

SABRTooth
Stereotactic Radiotherapy vs. Surgery in early lung cancer

• A study to determine the feasibility and acceptability of conducting a phase III randomised controlled trial comparing Stereotactic Ablative Radiotherapy (SABR) with surgery in patients with peripheral stage I nOn-small cell lung cancer (NSCLC) cOnsidered To be at Higher risk of complications from surgical resection.
• SABRTooth is funded by Research for Patient Benefit (NIHR RfPB) Programme Ref PB-PG-0613-31114

• The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health
Eligibility

- Peripheral (>2 cm from the main airways), Stage 1 (T1a1b, T2a, N0M0 < 5 cm), NSCLC
- Lung cancer MDT consensus is the patient is suitable for surgery but at higher risk of complications

Seen by Respiratory Physician for diagnosis. SABRTtooth discussed and information sheet provided

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Consent with Research Nurse or Respiratory Physician

Seen by Surgeon

Seen by Clinical Oncologist

Patient or clinician decides against randomised treatment

Follow-up visits at 6 weeks, 3, 6, 9, 12, 18 & 24 months post-treatment or until the end of follow-up period (6 months after last participant randomised). Questionnaire data administered via post at 15m and 21m post-treatment and OS data collected at the end of the trial via the NCDR.

Patient is invited to take part in Qualitative Feedback Interviews
SABRTTooth Recruitment as of 31 October 2016

SABRTTooth Overall Recruitment Chart

- Monthly Total
- Cumulative Recruitment
- Target recruitment

Overall target: 54

Open to recruitment: July 2015
Actual recruitment start: October 2016
Central Lung SABR

- Central “No-Fly Zone” from Timmerman et al JCO 2006
- However, others chose to fly into this zone
- Risk adapted approaches appeared to be safe...
Central Lung SABR

- NRG Oncology/RTOG 0814
- C-I Andrea Bezjak
- Toxicity G3 or higher
  - 10x 5 – none of 8
  - 10.5x 5 – 1 of 8 and was G5 i.e. fatal
  - 11x 5 – one of 14
  - 11.5x 5 – 4 of 38 and 2 fatal (G5)
  - 12x 5 – 5 of 33 and 1 fatal (G5)
  - All G5 were due to haemoptysis

Presented @ World Lung (Denver) 2015 + ESTRO (Turin) 2016
Central Lung SABR

- Are we causing cardiac toxicity?
- RTOG 0617 Bradley et al (Lancet Onc 2015)
  - Dose escalation resulted in worse outcomes
  - Suggested that this might be due to heart dose
- SABR Stam et al (ESTRO 2016)
  - Association between non-cancer death and dose to anatomical structure located at the top of the heart (left atrium and SVC)
Central Lung SABR

LungTech Stereotactic Body Radiotherapy (SBRT) of inoperable centrally located NSCLC: A phase II study in preparation for a randomized phase III trial

- CI Ursula Nestle
- European Study funded and opened in UK
- Centres: RMH, UCH, Christie, Leeds, Glasgow
- 60Gy in 8 fractions
- Strict Quality Assurance/Patient Selection
- Prospective data collection
- Translational Sub-studies
- Temporarily Closed pending review
SABR versus Conventional RT

SPACE – A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC

Jan Nyman a,*, Andreas Hallqvist a, Jo-Åsmund Lund b, Odd-Terje Brustugun c, Bengt Bergman a, Per Bergström d, Signe Friesland e, Rolf Lewensohn e, Erik Holmberg a, Ingmar Lax e

* Sahlgrenska University Hospital, Gothenburg, Sweden; b Trondheim University Hospital; c Oslo University Hospital, Norway; d Norrlands University Hospital, Umeå; and e Karolinska University Hospital, Stockholm, Sweden

- 102 pts
- 66Gy in 3 fractions versus 70Gy in 35 fractions
- No Difference in
- Progression Free Survival
- Overall Survival
- Tendency to improved disease control with SABR
- Better Quality of Life and Lower Side effects with SABR
Rationale for SABR/RT in addition oligometastatic disease
What is/are Oligometastases?

- Hellman and Wechselbaum proposed the notion of an “oligometastatic state” in 1995 (JCO Editorial)
- If we can eradicate sites of metastases might we delay systemic therapy, improve PFS/OS or possibly cure patients?

EASY- WE SHOULD JUST TREAT ALL PATIENTS WITH OLIGOMETASTASES WITH SABR.....

Outpatient treatment

- Acceptable toxicity
- High rates of local control
Combining SABR/RT with systemic therapies in stage IV disease
Do we have RCT evidence of a survival benefit of localised RT in Metastatic Lung cancer?
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• YES!!!
Do we have RCT evidence of a survival benefit of localised RT in Metastatic Lung cancer?

• YES!!!

• Extensive Stage SCLC
  • PCI in chemotherapy responders improved overall survival¹
Do we have RCT evidence of a survival benefit of localised RT in Metastatic Lung cancer?

- YES!!!
- Extensive Stage SCLC
  - PCI in chemotherapy responders improved overall survival\(^1\)
  - Consolidation thoracic RT improves PFS and 2 year overall survival\(^2\)

\(^1\)Slotman et al NEJM 2007
\(^2\)Slotman et al Lancet 2015
SABR or Conventional RT

• Why could SABR be better than conventional RT when combined with immunological therapies?
  • Very accurately delivered and typically small fields = Less collateral damage
  • Fewer fractions
  • ? More cell kill
SABR or Conventional RT

• Murine model evidence that high single fraction doses produce more CD8 T-cell infiltration in the tumour bed for colo-rectal tumour model\(^1\)

• Single high doses in combination with L19-IL2 increases CD4+ T cells in blood and more CD8+ T cells in abscopal tumours compared to fractionated RT\(^2\)

\(^1\) Filatenkov et al Clin Cancer Res 2015

\(^2\) Reckers et al Radiotherapy and Oncology 2015
SABR with Systemic Agents

• Combination of SABR with target therapies
  • e.g. SABR-PARP co-CI Gerry Hanna/Vicky Coyle
• Combination of SABR with immunological therapies
  • E.g. PRIMING CI Fiona McDonald,
  • MESO-PRIME co-CI Stephen Harrow/Fiona McDonald
  • SABR Avelumab co-CI Gerry Hanna + Kevin Franks
SABR PARP- A phase I study of rucaparib and stereotactic ablative body radiotherapy (SABR) to the lung in the treatment of oligometastatic disease

**Improve local control**
Particularly if defects in BRCA, FA or HR pathways

**Improve distant control**
Enhanced bystander/abscopal effects

**Protect normal lung tissue**
Reduction in normal lung tissue toxicity

- Significant body of *in vitro* and *in vivo* data demonstrating radiosensitising effects of PARPi
- Phase 1 trials ongoing combining PARPi & conventional external beam XRT

Slide courtesy of Dr Gerry Hanna Belfast
PRIMING: Pembrolizumab with SBRT for Advanced NSCLC

Primary Endpoint:
To establish MTD and RP2D that can be safely

Run-in Phase of Pembrolizumab
RT Phase: 54 Gy in 3 # over 1 week
Post-RT Phase: Pembrolizumab
D1 100 mg / D2 200 mg q3w
200mg q3w Pembrolizumab

Slide courtesy of Dr Fiona McDonald RMH
MESO-PRIME: Pembrolizumab with SBRT for Malignant Mesothelioma

Primary Endpoint:
To establish MTD and RP2D that can be safely combined

- Run-in Phase of Pembrolizumab
- RT Phase: 55 Gy in 5 # over 2 week
- Post-RT Phase: Pembrolizumab
- D1 100 mg / D2 200 mg q3w
- 200mg q3w Pembrolizumab

Slide courtesy of Dr Fiona McDonald RMH
Phase II multi-arm study of immunomodulatory agents in combination with RT for stage IV NSCLC

- Patients with stage IV NSCLC (include stage III patients ineligible for radical treatment?)
- Standard chemotherapy followed by stratification based on indication for palliative RT
- RT options: 20 Gy 5# to met(s); SABR to met(s); 36 Gy 12# to primary (if we include stage III)
- Immunomodulatory drugs; phase I RT combination data already available for several
- Likely to be different drugs for the different arms

SABR for Oligo-progression

- Small Single arm Ph2
- PD after 1st line chemo
- ≤ 6 sites of mets
- SABR to mets and erolotinib
- 2 episodes of G3 RT toxicity
- Median PFS 14.7mths OS 20.4 mths
HALT- Trial Flowchart

Advanced NSCLC 
EGFR / ALK + with response to TKI

TKI

Progression

Oligo-
Progression

Widespread 
Progression

Randomise (2:1)

SABR & 
continue TKI

Continue TKI

Primary Endpoint: 
Progression Free Survival

Target: 
120 patients

Slide courtesy of Dr Fiona McDonald RMH
Conclusion: UK is leading/contributing to Key SABR Research

Stage I NSCLC

• Alternative to surgery
• Is it safe for central disease

New options for stage IV lung cancer

• Ablative therapy for oligometastases
• Ablative therapy for oligo-progression
• Enhancing the effects of systemic agents
UK SABR Consortium Trials Update

Rushil Patel
UK National RadioTherapy Trials QA (RTTQA) group
Mount Vernon Cancer Centre
United Kingdom
A randomised trial of Conventional care versus Radioablation (stereotactic body radiotherapy) for Extracranial metastases

• **Aim**
  • To evaluate if the addition of SBRT to standard therapy improves progression free survival outcomes in patients with a limited burden of oligometastatic disease

• **Patient Eligibility**
  • Primary Breast, Prostate or NSCLC
  • Primary site must be controlled for 6 months (4 months for NSCLS)
  • ≤ 3 metastatic lesions (total)
  • A maximum of 2 different organ systems may contain metastases
CORE

• Trial opened 7\textsuperscript{th} October 2016
• Aims to recruit 206 patients
• Four sites have opened
  – RMH Fulham Road, James Cook, Nottingham, Mount Vernon
• Three patients have been randomised
CORE

• All 17 CtE centres have completed minimum QA required
• Several non-CtE centres are in progress
• A number of centres are close to opening (awaiting site agreements)
• International sites are in development
• A similar QA programme will be used
CORE & CtE

• Once the trial has opened at a centre, patients eligible for CORE will no longer be eligible for CtE
• CtE will close to all CORE eligible patients at all CtE sites on the 31st December 2016
Stereotactic Ablative Radiotherapy for Oligometastatic Non-small cell lung cancer a Randomised Phase III Trial

• Aim
  – To investigate the impact on overall survival of the addition of conventional RT and SABR/SRS to standard systemic therapy in the first line treatment of non-small cell lung cancer patients with one to three metastatic lesions.
Thoracic Safety Sub-study

• Aim
  – Assess toxicity of patients receiving SABR to thoracic metastases following treatment of the primary lung tumor with conventional RT

• Primary End Point
  – Grade 3-5 Radiation Induced Pneumonitis (RTPN) within 3 months post last dose of thoracic SABR treatment

• Secondary End Point
  – Other grade 3-5 RT adverse events
Thoracic Safety Sub-study

- TSSS patients can only be treated at selected centres
- TSSS patients must be prospectively reviewed by the TMG
- This will be reviewed after the first 20 patients
SARON

• Trial opened 11th August 2016
• Aims to recruit 340 patients
• Three sites have opened
  – Clatterbridge
  – James Cook UH
  – Barts
• Two patients have been recruited
• Hoping for 5 sites by the end of the year
SARON delays

- HRA approval processes
- NHS England - clarification on excess treatment costs
- Referral pathways may need to be setup for TSSS and any treatment sites awaiting QA approval
- UCL trials unit working with NHS England to facilitate this.
Quality Assurance Streamlining

• CORE
  – Centres need to be approved for two metastatic sites to open
  – QA is streamlined through CtE programme.
  – No additional QA required if already approved for CtE

• SARON
  – Conventional Lung streamlined through previous lung trials (IDEAL, I-START, Isotoxic) or ADSCAN trial
  – SABR streamlined through CtE programme
  – SRS streamlined through NHS England SRS programme, a benchmark is available for non English centres
The application of the £6m national allocation to support research trials in the use of Stereotactic Ablative Radiotherapy (SABR).

- Centres in England that are contracted to deliver SABR for patients with early non-small cell lung cancer
- Centres in England that are contracted to deliver SABR through the CtE programme
- SRS is restricted to SRS commissioned centres
The six clinical trials endorsed and supported by are:

- **SPARC**, for pancreatic cancer;
- **SARON**, for the treatment of the primary lung cancer (with SABR or conventional Radiotherapy) and oligometastatic disease from non-small cell lung cancer;
- **LungTech**, for non-small cell lung cancer;
- **ABC-07** for advanced biliary tract cancer.
- **CORE** study for oligometastatic disease from breast, renal, prostate, and non-small cell lung cancer.
- **PACE** study for early stage, organ-confined prostate cancer.
SABR Trials Funding (England)

NHS England are clarifying the position of these trials

• PERM
  – A Randomised Phase II Trial of Pembrolizumab and Radiotherapy in Melanoma

• HALT
  – Ablative Radiotherapy for Oligo-Progressive Disease (OPD) in Oncogene Addicted Lung Tumours
SABR Spine Audit
SABR Spine Audit

• Audit is currently under development by RTTQA, NPL and the UK SABR consortium QA sub-group
• Gafchromic film will be used to capture a 2D plane
• Point measurements will be taken in the Spine and Cord using Alanine and a detector
• 0.125cc, Microdiamond and Scintillation detectors are being evaluated
SABR Spine Audit

• Audit will compare measured readings with dose to medium and dose to water calculations where possible
• IGRT sub-study will be combined with the spine audit
Acknowledgements

RTTQA group
SARON TMG
UCL CTU
CORE TMG
ICR CTSU
Any Questions?