Introduction

- Radiotherapy is a primary, adjuvant or neoadjuvant treatment for a number of different cancers such as lung, glioblastoma, breast and prostate. Image-guided micro-irradiation (IGMI) is widely used to treat cancer patients providing more accurate treatment plans and reduced side effects.
- However in the preclinical setting the use of IGMI is less common with traditional irradiation studies utilising whole body irradiation with lead shielding attempting to focus the radiation to a specific area on the animal or simple single beam techniques.
- The development of the image-guided small animal radiation research platform (SARRP) allows the treatment of animal models of cancer more accurately and importantly, with planned protocols similar to those utilised in the clinic.
- Lung cancer is the largest cancer killer with poor 5-year survival rate. Non-small cell lung cancer (NSCLC) patients that have cancer more accurately and importantly, with planned protocols similar to those utilised in the clinic.
- Here we demonstrate the application of IGMI to treat subcutaneous xenograft tumours established from both cell lines and patient-derived material with little or no adverse effects, as well as the utilisation of the SARRP for in vitro screening.

Methods

- In vivo xenograft: Caucasian non-small cell lung cancer (NSCLC) PDX models, known as Lung in Oncology (LION) and part of our HuPrime® platform (Table 1), are maintained subcutaneously in nude mice (Hsd:Ola:MF1-foxn1-nu) admixed with a human stromal cell component (bone marrow-derived human mesenchymal stem cells, Scitcell). HCC827 and HCC827-ER1 cells were implanted subcutaneously in nude mice (Validated Cells™ in Hsd:Ola:MF1-foxn1-nu). Erlotinib was dosed at 25mg/kg po qD. Crotinib was dosed at 50mg/kg po qD. Tumour measurements and body weights were taken 3 times weekly and dosing initiated in both models when the tumours reached a mean volume of ~200mm³.
- In vivo Irradiation: Mice were anaesthetised and transported to the SARRP where CBCT images were acquired. Using the Murislice software the isocenter of the tumour was identified and aligned with the central axis of the beam. Fractionated irradiation was administered with the SARRP (225 kV peak X-ray beams, dose rate of 2.5 Gy/min) using collimators of various dimensions and a double beam (gantry position at 90° and 180°) under the guidance of the CBCT. A tolerability was performed initially to evaluate 3Gy/day x 5 days for 2 weeks.

Results: Tolerability

- Mice bearing subcutaneous NSCLC PDX tumours tolerated 2 cycles of 3Gy/day for 5 days using the SARRP.

Results: NSCLC PDX

- The SARRP integrates cone beam computed tomography (CBCT) imaging with high resolution (low imaging dose and 3D reconstruction) with radiation treatment (X-ray).
- Irradiation & imaging takes place in a chamber that incorporates a X-ray tube (middle), an imaging system (top) and an isocentre (bottom). The SARRP integrates cone beam computed tomography (CBCT) imaging with high resolution (low imaging dose and 3D reconstruction) with radiation treatment (X-ray).
- Image fusion options for easy target localization, dose planning and avoidance of normal organs at risk.
- High precision beam to achieve conformal dose distributions and clinical quality.
- Open platform to enable the addition of other imaging modalities for future research.

Abstract:

Treatment of patient-derived NSCLC xenograft preclinical models using image-guided small animal irradiation

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Background: SARRP features

- The SARRP integrates cone beam computed tomography (CBCT) imaging with high resolution (low imaging dose and 3D reconstruction) with radiation treatment (X-ray).
- Irradiation & imaging takes place in a chamber that incorporates a X-ray tube (middle), an imaging system (top) and an isocentre (bottom).

Results: Combination studies

- HCC827 NSCLC adenocarcinoma cell line harbours an activating EGFR mutation (delE746-A750) and was used to test the combination of the image-guided small animal radiation research platform (SARRP) allowing the treatment of animal models of cancer more accurately and importantly, with planned protocols similar to those utilised in the clinic.
- Lung cancer is the largest cancer killer with poor 5-year survival rate. Non-small cell lung cancer (NSCLC) patients that have cancer more accurately and importantly, with planned protocols similar to those utilised in the clinic.
- Here we demonstrate the application of IGMI to treat subcutaneous xenograft tumours established from both cell lines and patient-derived material with little or no adverse effects, as well as the utilisation of the SARRP for in vitro screening.

Conclusions

The SARRP platform allows the use of irradiation with anti-cancer agents in small animals with reduced side effects and improved outcome. This will allow these novel preclinical PDX models to be used effectively for drug discovery programmes to identify promising treatment options for clinical testing of cancer patients using either radiotherapy alone, or in combination with other agents.

Table 1: Summary of Caucasian NSCLC PDX models

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<thead>
<tr>
<th>HũId</th>
<th>LION number</th>
<th>Sub-type</th>
<th>Known Mutations</th>
<th>FGFR1, c-met</th>
<th>FGFR1 &amp; FGFR2</th>
<th>FGFR1 &amp; FGFR2</th>
<th>EGFR inhibitor</th>
<th>TcS response</th>
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<tr>
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<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Complete response</td>
<td></td>
</tr>
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Figure 1: External view of SARRP (left), internal view showing robotic stage, rotating gantry and X-ray tube (middle), isocentre identification using Murislice software with CT imaging (right).

Figure 2: Tolerability: % body weight measured during the study increased gradually as expected (data not shown) and no adverse effects were noted.

Figure 3: The effect of 3Gy/day irradiation on six PDX lines (dotted line indicates dosing events).

Figure 4: The effect of 3Gy/day irradiation on HCC827 & HCC-827ER1 subcutaneous xenografts in combination with Crotinib and Erlotinib.

Figure 5: The e...