Conclusion: PUMA can predict the interplay effect on SABR lung cancer patients and has the potential to be used as a routine method to ensure an appropriate low level of modulation on SABR lung plans independently of the energy.

Symposium with Proffered Papers: Lung - treatment intensification and individualisation II

SP-0239
Pre-clinical aspects of combining targeted agents and radiotherapy
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Preclinical evaluation of novel anticancer agents combined to Ionizing Radiation (IR) is a key step in the generation of a sound rationale for further transfer towards the early clinical phases. Animal models should allow the minimal assessment of the toxicity hazard and provide significant signs of increased anti tumor efficacy, both required to address their clinical relevance, i.e. the therapeutic ratio of a candidate future combination. This assumption is clearly challenged by the major discrepancy between the amount of combinations suggested by preclinical data in the last decade and the fact that platinum based combinations remain the mostly widely used agents in the management of lung tumors. This not only illustrates the difficulties in funding the continuum from promising preclinical data to clinical steps, but also underscores the relatively low relevance of our preclinical models. Certainly, one of the reasons for this gap is the inhabitation of our preclinical models to keep up with the changes in the mutational landscape of lung cancer. Another major aspect is that most models used so far include immunocompromised models, which fail to recapitulate the importance of the tumor stroma in the processes of radiation response. The precise correlation between the preclinical judgment criteria and the medical need is also key: while most preclinical papers focus on tumor growth delays, the clinical need is to increase local control and to minimize the onset of metastasis. Lastly, the potential deleterious impact on normal tissues, both acute and long term, should also be properly evaluated at the preclinical stage to increase the accuracy of this appraisal. Preclinical models should also try to address the current challenges of the biomarker era and suggest in which biological context, and which criteria may be used to define the optimal biological context for patient selection. Importantly, integration of cisplatinum based chemotherapy as a reference may be useful for proper assessment of potential clinical gains. To conclude, immunological and vascular parameters can be dramatically affected by fractionation, fractionating irradiation is thus important for the evaluation of candidate combinations. Genetically engineered mice models and orthotopic murine models in immunocompetent recipient mice should markedly contribute to an improvement of the output of these murine models and eventually increase the success rates of future clinical trials while avoiding the transfer of ineffective or hazardous combinations to the patient.

SP-0240
Targeted agents, systemic therapy and radiotherapy of non-small cell lung cancer: clinical evidence
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Non-small cell lung cancer (NSCLC) is a group of different histologic tumor types with diverse molecular aberrations. Lung adenocarcinomas are now classified according to driving molecular abnormalities (mutations, rearrangements or amplifications), which can be identified in more than half of tumors, leading to effective systemic therapies in many of these patients. In contrast to that, evidence for presence of such abnormalities in squamous cell lung carcinomas is less clear. Successful combination of targeted therapies, chemotherapy and radiation in early NSCLC should be taken into account in the context of molecular drivers. In oncogenic-driven stage III NSCLC, it is likely that effective systemic treatment will be combined with radical radiotherapy or radiochemotherapy as a sequential treatment, although evidence for such approach is currently lacking. RTOG 1306 phase II clinical trial is currently randomly allocating stage III patients with tumors showing EGFR mutations or ALK rearrangements to either radiochemotherapy alone (control group) or 12 weeks of erlotinib (EGFR cohort) or crizotinib (ALK cohort) followed by definitive radiochemotherapy. In non-oncogene addicted NSCLC, incorporation of targeted therapies into radiochemotherapy schedules is very difficult to predict preclinically, as demonstrated by several examples, including negative results of the RTOG 0617 trial. This trial failed to show any benefit from the addition of cetuximab, a monoclonal antibody targeting EGFR, into radiochemotherapy in stage III NSCLC. Lack of good prediction of clinical data may result from complex interactions among targeted agents, chemotherapy, and radiation. One of the most promising strategies for the future is related to the success of immune checkpoint inhibitors, which show considerable promise as adjuvant systemic treatment after definitive radiochemotherapy. Optimization of combined radiation and chemotherapy programs is still a matter of ongoing discussions and investigations. Although concurrent radiochemotherapy is a standard of care in fit stage III NSCLC patients, sequential treatments with cytotoxic agents followed by either hypofractionated or hyperfractionated accelerated radiotherapy schedules are currently revisited.

OC-0241
Can dose escalation be consistently carried out in a multicentre trial? QA results for IDEAL-CRT and I-START trials
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Purpose/Objective: IDEAL-CRT and I-START are phase I/II trials investigating isotoxic dose escalation in patients with stage IIa-IIb non-small cell lung cancer. In both trials the
OC-0242

A randomized phase II trial of concurrent chemo-RT of oral vinorelbine and 60 Gy or 66 Gy, in locally advanced NSCLC was performed every 3 m starting 1 m after commencing radiotherapy for 2 y and then every 6 m. As part of the protocol, a PET-CT scan was conducted 9 m after randomization. The primary endpoint was the Local Progression Free Survival Rate (LPFSR). The goal of the study was within the 95% confidence interval (95%CI) to have a LPFSR at 9 m of 80%. Log rank tests were used to test survival.

Results: In arm A and B, 59 and 58 patients were eligible. The two arms were well balanced. The minimum and median potential follow-up was 14.5 and 32.6 m, respectively. The median number of Nav was 18 x in arm A and 20 x in arm B. Of the patients, 10% had ≤12 x Nav. The LPFSR at 9 m was in arm A: 54% (95%CI: 43%; 64%), and in arm B: 60% (95% CI: 49%; 71%), and the LPFSR at 1 and 2 year was 40% and 32% in arm A, and 49% and 44%, in arm B. The median OS was 23.3 m in arm A, and 25.3 m in arm B. The median OS was comparable reference group.

Conclusions: Protocol deviations for IDEAL-CRT and I-START were seen in less than 4% and 6% of patients respectively. Complex dose escalation trials can be carried out in a multicentre setting provided there is a comprehensive pre-trial and on-trial QA programme in place.

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