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Intravital Imaging of Cancer Invasion and Resistance to Therapy

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The tumour microenvironment contributes to cancer invasion, growth and survival and thereby impacts tumour responses to therapy. Using infrared-excited multiphoton microscopy in orthotopic fibrosarcoma and melanoma xenografts, we here identify a novel radio- and chemoresistance niche consisting of invading tumour cell strands consisting of several hundred connected cells located within collagen-rich stroma nearby blood and lymph vessels. Despite normoxia, perivascular invasion strands were resistant to high-dose hypofractionated irradiation which otherwise was sufficient to induce regression of the tumour main mass. This invasion-associated chemo- and radioresistance was sensitive to the simultaneous inhibition of β1 and β3 integrins by RNA interference or combined anti-β1/aV integrin antibody treatment leading to proliferation arrest, anoikis induction and subtotal to complete regression of both tumour lesion and invasion strands. Thus, collective invasion is an important invasion mode in solid tumours into a microenvironmentally priviledged perivascular survival niche which conveys radioresistance by integrin-dependent signals.

Special Session (Tue, 27 Sep, 11:30−12:30) **Innovations in Early Clinical Trials**

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Phase 0 Vs. Phase I − Ethics, Regs and Feasibility

Abstract not received

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Innovative Models to Optimize Phase I Development of Novel Anticancer Agents

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Increasingly in solid tumour and hematological oncology novel drugs are being developed that lack direct cytotoxic anticancer activity. Novel drugs often interfere with transmembrane or intracellular targets, for example those with tyrosine kinase activity. In addition, soluble factors are targeted thereby preventing activation of transmembrane receptors. These drugs do not have classical dose-limiting toxicities, such as bone marrow suppression and mucosal toxicity, but a variety of other and sometimes severe toxicities. These developments call upon novel development strategies. Based upon the chemical characteristics and preclinical safety profile sometimes healthy volunteer studies can be performed to speed up dose-finding, for surrogate target engagement and other pharmacological studies prior to studies in patients (then so-called phase Ib studies). Other starting dose-levels in patients can be derived from preclinical and healthy volunteer studies speeding up clinical development. Patient selection based on biomarker profiling in tumour tissue already early in phase I may be indicated for proof of principle in target tumour tissue. This necessitates tumour sampling in the interest of drug research. In addition, minimally invasive imaging by PET/CT may be helpful in obtaining proof of principle or to demonstrate antitumour activity where RECIST may not be informative.
Besides these developments phase 0 (zero) studies can be implemented for selection of the optimal clinical candidate, for pharmacodynamic studies and imaging. These studies should help to improve efficacy of the clinical phase of drug development by preventing failures due to poor ADME (absorption, distribution, metabolism, excretion) and lack of target engagement.
In addition, new algorithms may be used for combination strategies of so-called targeted agents in early clinical studies improving the efficacy of development of novel combinations.

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Tackling Futility With Adaptive Designs

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Background: More than 800 drugs are in development in oncology, most being molecularly targeted agents (MTA), making early “go/ no go” decision crucial. Futility can then be seen as the absence of detection of activity bearing toward early discontinuation of the clinical development.
Two key aspects strongly contribute to the high attrition rate observed in oncology.
– Absence of selection of the adequate population
– Lack of sensitive endpoints
Using the toxicity as a unique endpoint for identifying the optimal dose or using the overall response rate for identifying treatment activity fails to address both concerns, especially with MTA where the optimal dose may be quite different from the MTD. Stopping trials early for lack of activity based on these endpoints is an inefficient strategy.
Method: An alternative promising endpoint is the tumour growth. More generally continuous pharmacodynamic markers of treatment activity would bring more sensitive information. This refined information makes it possible to draw additional results from early phase trials. Adaptive designs then afford a setting to reassess the trial objectives (modify the dose, enrich the population, interupt the trial) based on estimates of both the toxicity and the activity endpoints.
In this communication, we show how statistical methods based on continuous endpoints enable to rapidly detect absence of activity in the investigated population. Using simulations of realistic scenarios of dose-toxicity-activity relationships in the framework of phase I/II trials, we illustrate the benefit of this approach. We also quantify the risk of erroneously concluding to the absence of activity when there is really one. Conversely, we provide the risk of false positive conclusions.
Conclusion: Using continuous endpoints bring much more information than binary endpoints. Although tumour growth is probably not a valid surrogate marker for treatment benefit, this is expected to be a valid marker to compare dose levels, to compare sub-populations and to identify absence of treatment effect in the investigated population as early as phase I or II clinical phases. However, these good performances rely on the fact the sample includes some responders.