status, co-morbidity, polypharmacy, poor nutritional status, diminished cognitive function and altered emotional status). It has been shown that patients classified as "frail" from the CGA may present more post-operative complications when compared to the "not frail" ones. The Pre-operative Assessment of Cancer in the Elderly study (PACE) has identified factors which have a negative impact on short-term outcomes after cancer surgery in the elderly. 400 patients over the age of 70 with various types of cancer had a geriatric assessment performed using tools to assess co-morbidity, activities of daily living, cognitive function, fatigue, depression and Eastern Cooperative Oncology Group Performance Status (ECOG PS). The American Society of Anesthesiologists (ASA) classification, Physiological and Operative Severity Score for enumeration of Mortality and Morbidity (POSSUM), and the Portsmouth variation of POSSUM were incorporated into the questionnaire. Disability, measured as dependency in instrumental activities of daily living (IADL), correlated with a 50% increase in the relative risk of experiencing post-operative complications. PACE concluded that IADL, fatigue (as measure by the Brief Fatigue Inventory) and ASA score were the strongest predictors of poor post-operative outcomes. Because of our poor understanding of frailty in onco-geriatric series, elderly cancer patients are often excluded from clinical trials. This aggravates the lack of evidence-based knowledge and perpetrates mis-management. Even when they are included, there is often insufficient baseline information about PS, co-morbidity, cognitive state and nutritional status making accurate interpretation of results difficult. The implementation of these tools into surgical practise will allow better framing of the cohort undergoing surgery, resulting into more comparable outcomes within clinical trials. The CGA is also a useful adjunct to the consent process. Routine assessment of frailty in elderly patients is warmly recommended before cancer treatment, either through CGA or via a quick screening tool, e.g. Groningen Frailty Indicator. This will allow tailoring the appropriate treatment after evidence-based consenting; it will also enable one to correct for differences in pre-operative variables, allowing more accurate comparison of results within trials. The result of this knowledge will permit drafting guidelines and treatment protocols and, eventually, an improved standard of care for the elderly.

165 INVITED

Systemic therapy

M. Extermann[1]. [1]*Moffitt Cancer Center, Senior Adult Oncology, Tampa, USA*

This presentation will review the three main modalities of systemic treatment in the elderly: hormonal therapy, chemotherapy, and targeted therapies. Hormonal therapy is usually considered a well tolerated approach but we will review some aspects of the side effect profile of particular importance in the elderly, such as musculoskeletal, vascular, and cognitive side effects. The proper prescription and delivery of chemotherapy in older patients is a major dilemma for oncologists. Recent research can however help us target more precisely our treatment to the individual patient, both in terms of tumor and host. This fits in the lines of a personalized cancer care approach. When targeted therapies first appeared, large hopes were held that they would provide low toxicity treatments to older patients. This hope has only been partially fulfilled. Nevertheless, such therapies have increased our options for designing the care of older cancer patients. It is important to recognize that host senescence can significantly affect the mechanism of action of targeted therapeutic approaches. As our longevity increases, the oldest old (patients aged 85 and older) are increasingly being seen in oncology clinics. There is a dearth of prospective data to guide treatment in this population, but cohort data can provide us with some insights and will be reviewed in this presentation.

Scientific Symposium (Tue, 22 Sep, 14:45−16:45)
Biomarkers in early clinical drug development

166 INVITED

Biomarkers and personalized models in oncology drug development

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Biomarker discovery in oncology has been robust but development has been plagued by the need to validate these markers at various key phases. Target discovery in tumors and or in cell lines with differential sensitivity usually starts the process. Then, simple cutoffs must first be identified and established in samples of convenience. Robust technology assessment and implementation must take place to ensure reliable and accurate results. Retrospective clinical analysis must be done, testing the biomarker in key studies where clinical drug sensitivity is established. Eventually, a prospective clinical analysis must be performed to validate use of the marker, though this can be done in prospectively collected samples. Finally, either a laboratory or a commercial entity must offer the predictive biomarker to ensure its integration in the clinic. We will discuss various biomarkers including key genetic and epigenetic markers in development and those already in the clinic. We will also discuss the development of new predictive personalized models which are at the nexus of integrating biomarkers and drug testing.

Preclinical oncology drug development typically originates from high passage number immortalized cell lines. While information from these models is useful in discovery and initial proof-of-concept studies, their clinical relevance is often limited due to alterations and adaptations from successive passages in tissue culture and animals. Preclinical personalized models established from donor patient tumor fragments passaged only a few times in vivo may better represent clinical disease. Following establishment, models can be characterized at the molecular level and then correlated with in vivo sensitivities of various agents and clinical information from patient donors as well as current standards of care. Molecular characterization studies identified known mutations in several signaling molecules important in cancer progression as well as novel markers of sensitivity and resistance to standard agents. These low passage models offer an alternative to standard xenografts and may be more representative of clinical disease. Data collected from molecular characterization and in vivo evaluation of these models will aid greatly in development of novel agents and predictive biomarkers.

167 INVITED

The need for robust statistical designs to bring biomarkers to the clinic

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New technology and understanding of tumor biology make it increasingly feasible to develop prognostic and predictive biomarkers that provide information about which patients require systemic therapy and which are most or least likely to benefit from a specific treatment. Using such biomarkers to target treatment can greatly benefit patients, reduce societal medical costs and improve the chance of success in new drug development. Although it is often said that use of genomic biomarkers can make drug development simpler, quicker, and cheaper, co-development of new drugs with companion diagnostics often increases the complexity of drug development.

There is considerable confusion in the literature on the role of biomarkers in drug development and how such biomarkers should be "validated". In this presentation we will distinguish the different types of applications of biomarkers, will clarify that "validation" means "fit for purpose" and will identify different steps of validation for different biomarker indications. We will provide a roadmap for the development of candidate predictive biomarkers and for the use and evaluation of such biomarkers in phase III trials of new drugs. We will address some of the difficulties in development of predictive biomarkers prior to their use in phase III trials. Several strategies for development will be described and critically discussed. Sample size requirements for development of predictive biomarker candidates and the implication of biomarker development on the structure of early clinical trials will be addressed. Reprints of some relevant publications are available at http://brb.nci.nih.gov.

168 INVITED

Circulating tumour cells as biomarkers in clinical trials

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Circulating tumor cells (CTC) are thought to represent the "leukemic phase" of solid tumors. Their isolation, separation and enumeration can now be reproducibly performed by validated assays utilizing multi-parameter cytometry. Several isolation and quantitation assays have been described. CTC have been shown to be most commonly detected in breast and prostate cancer and not detected in healthy volunteers. The presence of CTC associates with more advanced stage, but may also reflect disease biology. Three trials in patients with advanced breast, prostate and colorectal cancers have shown that patients with a CTC count above a predefined threshold ($\geqslant$5 in breast and prostate cancer, $\geqslant$3 in colorectal cancer) have a poorer overall survival. Overall, these studies showing that patients with higher CTC counts both pre- and post-treatment have poorer overall survival have clinically qualified this assay as a prognostic biomarker and have led to its FDA clearance. These studies also suggest that changes in CTC counts following treatment could potentially be utilized to guide changes in treatment. These data support the further evaluation of CTC as potential intermediate endpoints of treatment outcome.

CTCs retain many molecular characteristics of the primary tumor and its metastases, and can be used to examine the presence of a target or its loss in tumor cells by for example fluorescent in situ hybridization (FISH), sequencing or by immunofluorescence. Analyses of tumor cell specific changes such as mutations or translocations could be useful, allowing a better understanding of mechanisms of resistance or susceptibility to treatment with novel agents. Limitations to these studies, however, may include RNA degradation and contaminating WBC RNA.
Overall, it is envisioned that CTC biomarkers will play an important future role in drug development.

169 INVITED

Genomics in early clinical trials

L. Pusztai[1]. [1]*UT M. D. Anderson Cancer Center, Breast Medical Oncology, Houston Texas, USA*

It is common to employ gene expression profiling as a predictive marker discovery tool in Phase II clinical trials. However, there are several reasons why this supervised approach to predictor discovery may not yield reliable predictors. The multiple comparison problem, inherent to microarray analysis, leads to a large number of nominally small p-values, many of which are due to chance. Another confounder is that clinically important phenotypic characteristics (e.g. histologic grade, estrogen receptor status of breast cancer) are often associated with coordinated expression of thousands of genes. A simple comparison of transcriptional profiles of breast cancers that respond to preoperative chemotherapy with those that did not will reveal many differentially expressed genes. However, most of these genes will reflect the gene expression differences that underlie the phenotypic differences between the 2 response groups. Since responses are more frequent in high grade, ER-negative cancers compared to low grade and ER-positive tumors, the resulting pharmacogenomic response predictors often represent a predictor of clinical phenotype and may provide only modest added predictive value. The often small gene expression differences that are specific to responders and non-responders are easily masked by the large-scale differences due to any phenotypic imbalance between the response groups and the often small sample size of these discovery studies precludes meaningful adjustment for these confounders. Therefore, candidate predictive marker testing, as opposed to discovery, may be more efficient in conjunction with Phase II clinical trials. Usually, enough is known about the mechanism of action of most new drugs that one could rationally propose at least one or more response predictors. Conceptually, testing a response predictor in a prospective clinical trial is no different from testing a candidate drug in a therapeutic study and a 2-step, Phase II design can easily be adopted for a parallel, multi-arm, simultaneous marker and drug evaluation program.

References

Pusztai L, Anderson K, Hess KR. Pharmacogenomic predictor discovery in phase II clinical trials for breast cancer. Clin Cancer Res 13(20):6080−86, 2007

170 INVITED

Clinical biomarkers and imaging for radiotherapy-induced cell death

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Radiation, like most anti-cancer treatments, achieves its therapeutic effect by inducing different types of cell death in tumors. To evaluate treatment efficacy a variety of routine anatomical imaging modalities is available. However, changes in tumor function (*e.g.,* metabolism, proliferation, hypoxia) often precede these volumetric alterations and may reflect tumor responses to treatment more accurately. Therefore, reliable biomarkers and imaging modalities that could assess treatment responsiveness in an early phase would be very useful to identify responders and/or avoid ineffective, toxic therapies. A better understanding of cell death mechanisms following irradiation is essential for the development of such tools. This has become even more important with the recent introduction in clinical protocols of targeted biological agents that modify the radiation response at different levels.
The currently available assays to detect the most prominent types of radiation-induced cell death (apoptosis, necrosis, mitotic catastrophe, autophagy and senescence) *in vivo* and, if applicable, *in vivo*, will be presented in short. Two examples of non-invasive imaging techniques that allow visualization and quantification of radiation-induced cell death *in vivo* will be discussed in more detail: ^{99m}Tc-Annexin V scintigtaphy (TAVS) and ^{99m}Tc-methoxyisobutylisonitrile (MIBI) SPECT.
In a series 61 patients (NHL n = 27; HNSCC n = 16; NSCLC n = 16; SCLC n = 1; sarcoma n = 1) treated with low dose (2x2 Gy) involved-field radiotherapy (n = 27), cisplatin-based concurrent chemoradiotherapy (n = 16) or cisplatin-based chemotherapy (n = 18), we found a significant correlation between tumor TAVS uptake within 24−48 hours after start of treatment and outcome. More recently, we established a significant correlation between pre-chemotherapy MIBI uptake and tumor size change after 2 cycles of chemotherapy in 11 patients with advanced NSCLC.
The predictive value of these tests might help to design novel (combined modality) strategies and evaluate treatment effects at an early stage. Clearly, additional and more specific methods are needed for accurate patient selection to ensure optimal treatment and limit side effects.

Scientific Symposium (Tue, 22 Sep, 14:45−16:45)
Refining treatment and the cost of the cure − lessons from soft tissue sarcoma in young people

171 INVITED

Stratifying treatment for rhabdomyosarcoma

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All current clinical trials utilise some combination of the best known prognostic factors to stratify treatment intensity for patients with good or poor predicted outcomes. Such an approach is used as much to avoid over treatment of patients with a good chance for cure, as to improve cure rates for patients with less favourable disease.
Experience has confirmed the relevance of a surgical–pathological classification which groups patients according to the extent of the extent of disease remaining after the initial surgical procedure(s) but before beginning chemotherapy.
All groups are currently using the IRSG [Intergroup Rhabdomyosarcoma Study Group] surgical and pathologic grouping system with sometimes light differences.

i. Localized tumour, removed with pathologically clear margins and no regional lymph node involvement
ii. Localized tumour, grossly removed with (a) microscopically involved margins, (b) involved, grossly resected regional lymph nodes, or (c) both
iii. Localized tumour, with gross residual disease after grossly incomplete removal, or biopsy only
iv. Distant metastases present at diagnosis

However, there is a need for a pre-clinical staging system that did not depend on the surgeon's decision or on pathologic assessment of the specimen. Moreover, the great majority of patients (approximately 75%) have macroscopic residual disease (IRS Clinical Group III) at the primary site at the start of chemotherapy.
The TNM system built by the SIOP [International Society of Pediatric Oncology] and UICC [Union Internationale Contre le Cancer] was validated by many studies. It includes the evaluation of site of the local extension of the disease (T1 Confirmed to anatomic site of origin and T2 Extension to surrounding tissue), the size of the tumour (<5 cm or $\geqslant$5 cm), the regional nodal involvement (N0 Regional nodes not clinically involved, N1 Regional nodes clinically involved by neoplasm) and the presence or absence of metastatic disease (M0 No distant metastasis, M1 Metastasis present).
Last but not least additional prognostic influence of site of the disease, histological subtype and patient age adds to the complexities of treatment stratification.
Recently both IRSG and European Paediatric Soft tissue Sarcoma Group (EpSSG) have reevaluated and updated their staging systems. They take into account additional information to the TNM and IRS staging systems: patient age, histology and tumour site. They are the bases of the risk grouping systems currently used to stratify the chemotherapy as well as the indications of radiation therapy. Concordances and differences between these staging systems will be presented.

172 INVITED

Estimating the total burden of therapy in children treated for rhabdomyosarcoma

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Cure rates of over 70% are currently achieved for patients with non metastatic rhabdomyosarcoma (RMS) but young age at diagnosis (median 5 years) and the divergence of clinical presentation at many different